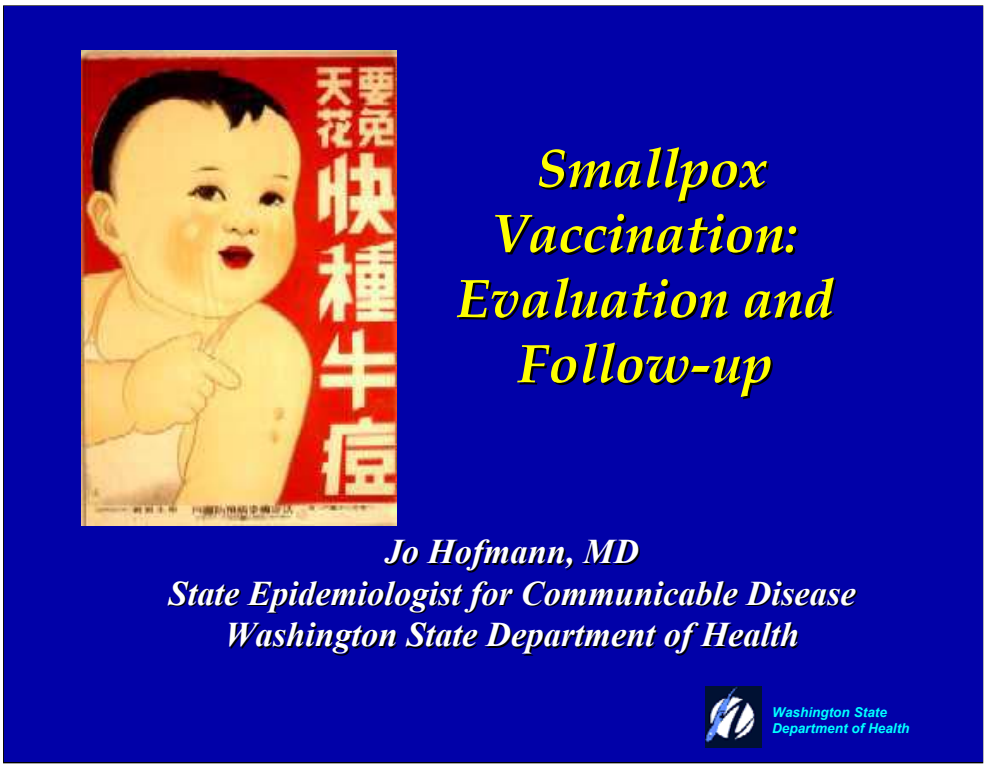
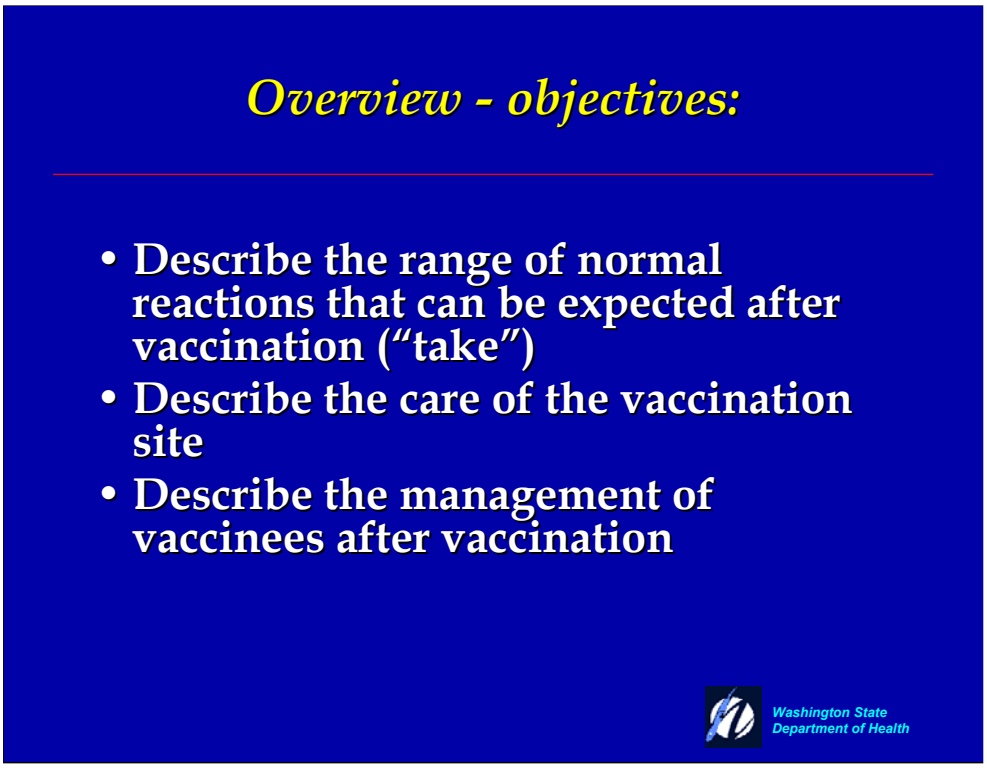


During the next hour, I will review information clinicians need to provide follow-up care to individuals who have received smallpox vaccination, including vaccination site care, infection control, and recognition of normal reactions to smallpox (vaccinia) vaccination. In the second section of my talk, I will review recognition and management of smallpox vaccine adverse events. In Washington, vaccination clinics for public health staff will begin February 20, and those for hospital staff will begin later in March.



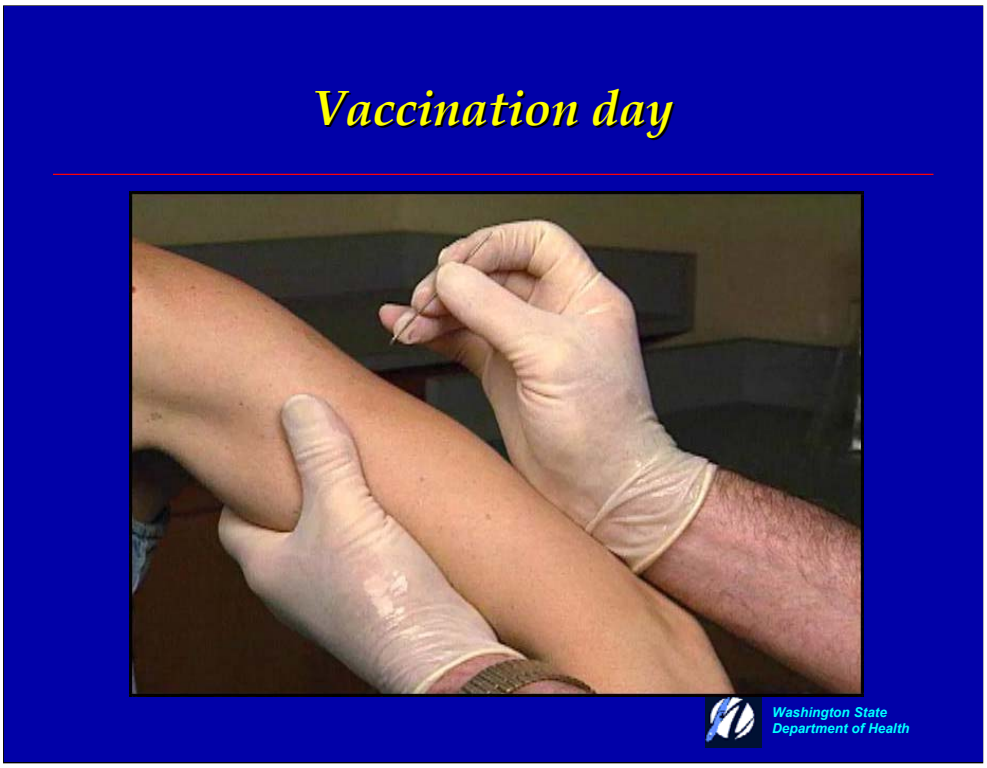
The objectives of this part of the presentation are to 1) describe the range of normal reactions that can expected after vaccination, including immune response, or take; 2) Describe care of the vaccination site, both for personnel who provide direct patient care and those who don't, and 3) describe the management of vaccinees after vaccination, including proper infection control and documentation of take.

Because most of us are not familiar with the use of smallpox vaccine, it's important to learn to differentiate between normal reactions that should be managed expectantly and those which may require specific treatment.

A quick review of vaccine - Wyeth Dryvax® smallpox vaccine contains vaccinia, a poxvirus related to variola, the smallpox virus. This is a live vaccine that was manufactured and frozen in the 1970s.

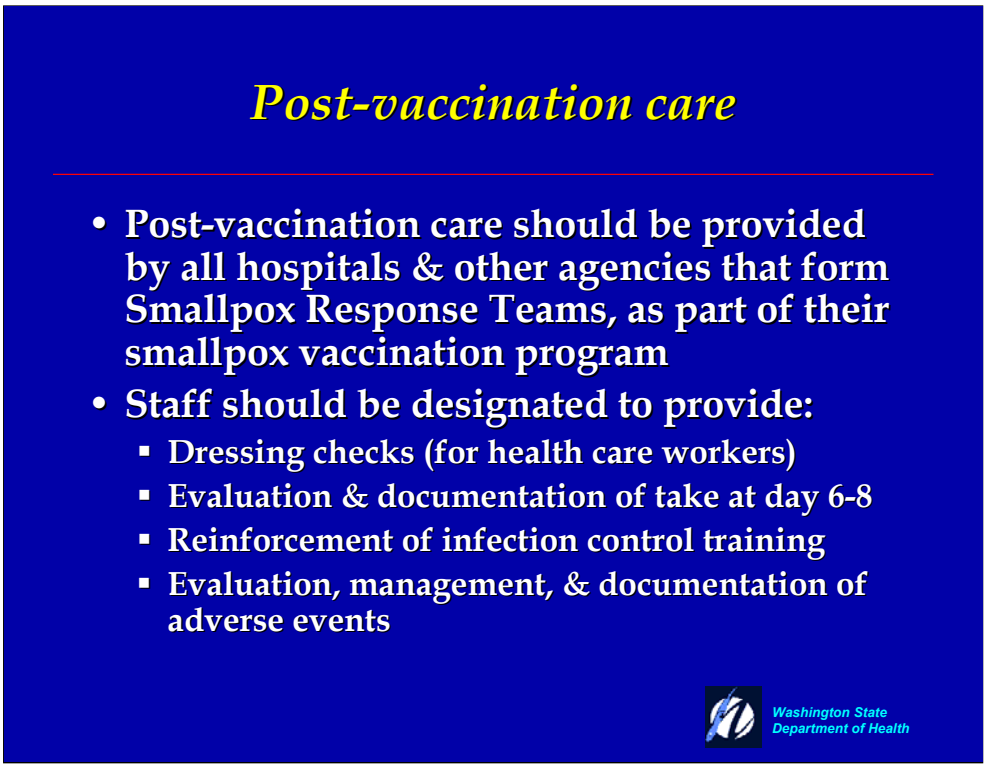
Routine vaccination in the U.S. ceased in 1972, so that most Americans under the age of thirty have never been vaccinated. The vaccine is derived from dried calf lymph, and contains the antibiotics polymixin B, streptomycin, neomycin and chlortetracycline. The diluent is glycerin with phenol as a preservative, and the vaccine does not contain thimerosal.

Vaccination is performed by scarification – inoculation into the epidermis with 3 or 15 jabs of a special bifurcated needle. The kit containing the needles, diluent and vaccine is licensed by the Food and Drug Administration (FDA), and the use of the needle has been approved by the Occupational Health and Safety Agency (OSHA). The vaccinia contained in this vaccine is the New York City Board of Health (NYCBOH) strain.



On the day of vaccination, the vaccinee will be given a Smallpox Vaccination Diary which asks them to keep track of any vaccine-related symptoms they may have during the 4 weeks following their vaccination. They are also given instructions on where and when to report for their take evaluation, and they are given a temporary immunization card that will be completed after their take is read. In addition, they will be given information about who to contact if they are concerned about a possible vaccine-related adverse event or have any concerns about their vaccination, and they will be provided with dressing kits and care instructions for their vaccination site.

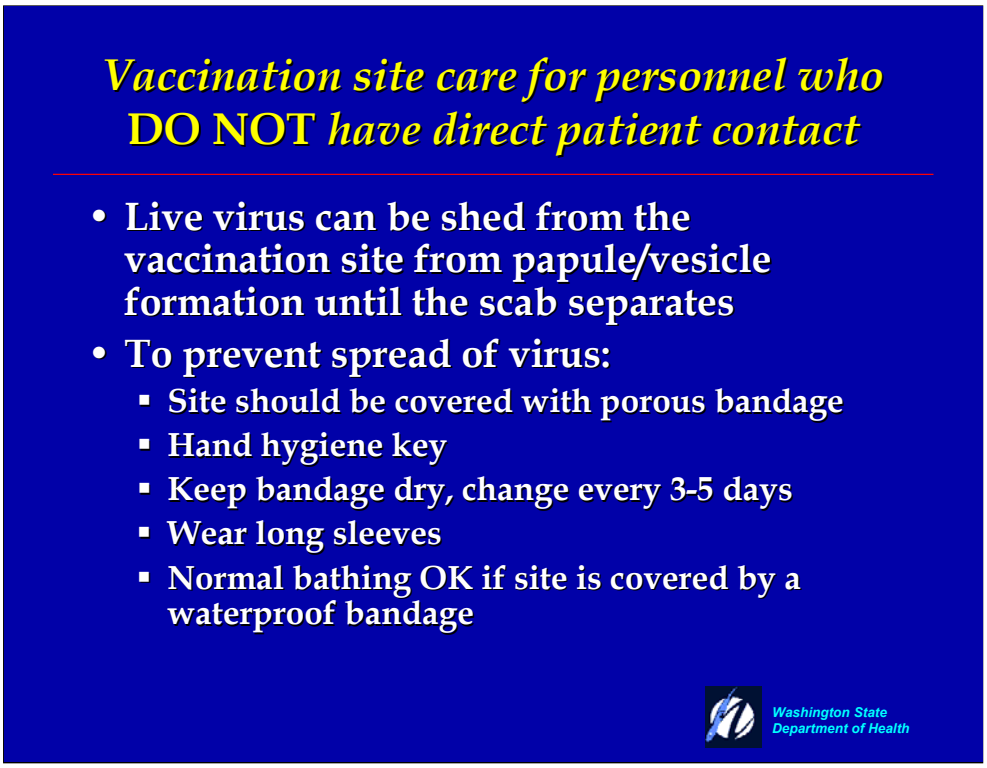
Between days 21-28, or after their vaccination site has healed, the vaccinee will be asked to report to their take monitor whether or not they had any problems and when their scab separated. At that time, they will turn in their diary. Data from these diaries will allow us to monitor vaccine safety and the impact of vaccination on time lost from work.



Post-vaccination care should be provided by all hospitals and public health agencies that form Smallpox Response Teams, as part of their smallpox vaccination program.

Staff should be designated to provide care to vaccinees, including regular dressing checks for those providing direct patient care, evaluation and documentation of take at day 6-8, reinforcement of infection control training, as well as evaluation, management, and documentation of vaccination adverse events. Ideally, staff providing this care would also be vaccinated, however, with proper infection control, it is not necessary that those checking or changing dressings, or managing adverse events be vaccinated.

Follow-up can be provided by a variety of licensed clinicians, depending on resources: nurses, physicians' assistants or physicians involved in infection control or occupational health, clinic, nursing or emergency room staff. Care should be available to workers on all shifts as needed.



First I'll discuss vaccination site care for personnel who do not have direct patient contact.

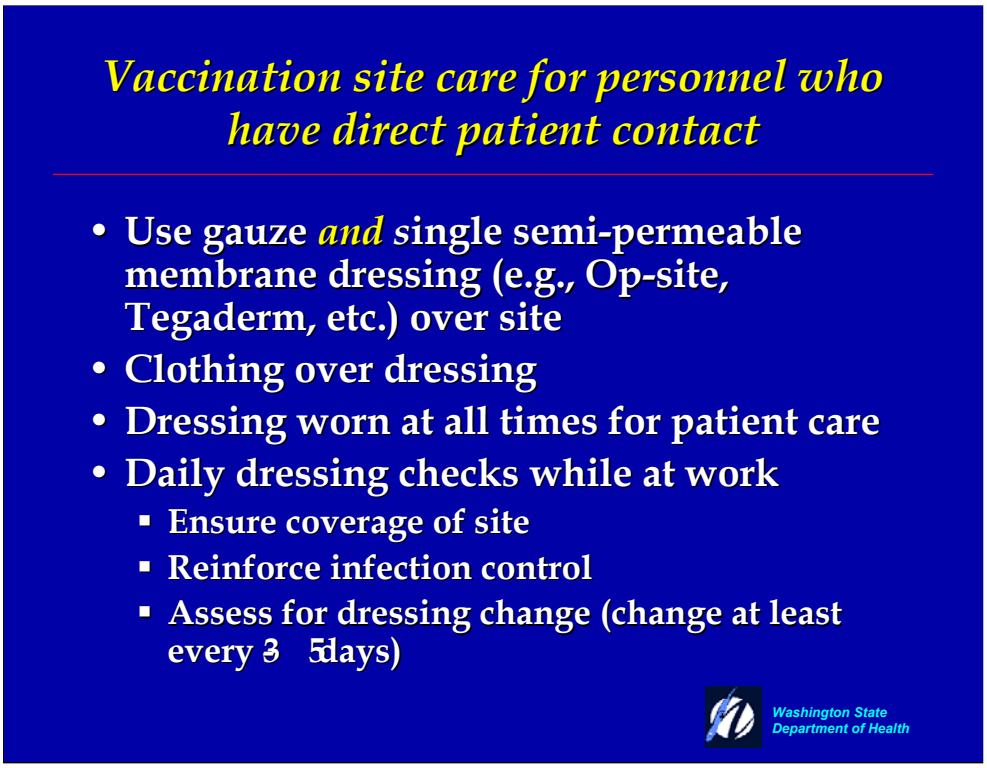
Live vaccinia virus can be shed from the vaccination site from the time a papule or vesicle develops (2-5 days after vaccination) until the scab at the site separates from the skin (21-28 days after vaccination). The virus is not shed from other sites, like the nose or throat. During this time, care must be taken to prevent transmitting the virus to another area of the body or to another person. When virus is spread to another person, this is called secondary, or contact vaccinia. When we routinely vaccinated children against smallpox, most cases of contact vaccinia occurred among household members having close contact with kids who had recently been vaccinated.

So, to prevent spread of the virus, the vaccination site should be covered with a porous bandage, like gauze, to absorb exudate, until the scab has separated and the underlying skin has healed. Keep the bandage dry and change it if it becomes wet, or at least every 3-5 days. In addition, wearing long sleeves may provide additional protection against spreading virus from the vaccination site. No salves or ointments should be used on the vaccination site.

Hand hygiene is key - washing hands with soap and water or using alcohol-based hand-rubs after contact with the vaccination site or dressings is the most important method to prevent the spread of vaccinia from the vaccination site.

Contaminated bandages and the scab, when it separates, should be placed in sealed plastic bags before disposal in the trash. In health care settings, contaminated trash can be disposed of in a biohazard bag. In households with pets or young children, any contaminated trash should be placed in covered containers. Clothing, towels, sheets, or other cloth materials that have had contact with the site can be decontaminated with routine laundering in water with detergent and/or bleach.

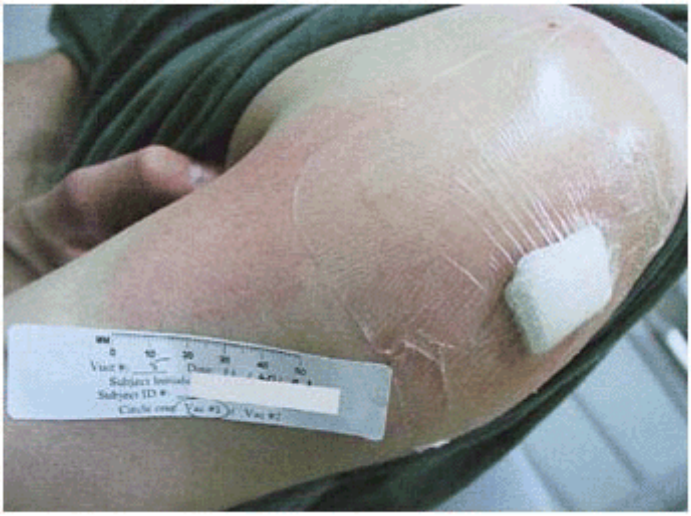
Normal showering or bathing is OK if the site is covered by a waterproof bandage. It's probably not a bad idea to avoid contact sports, communal showers, pools and baths during the time that the site can shed virus.



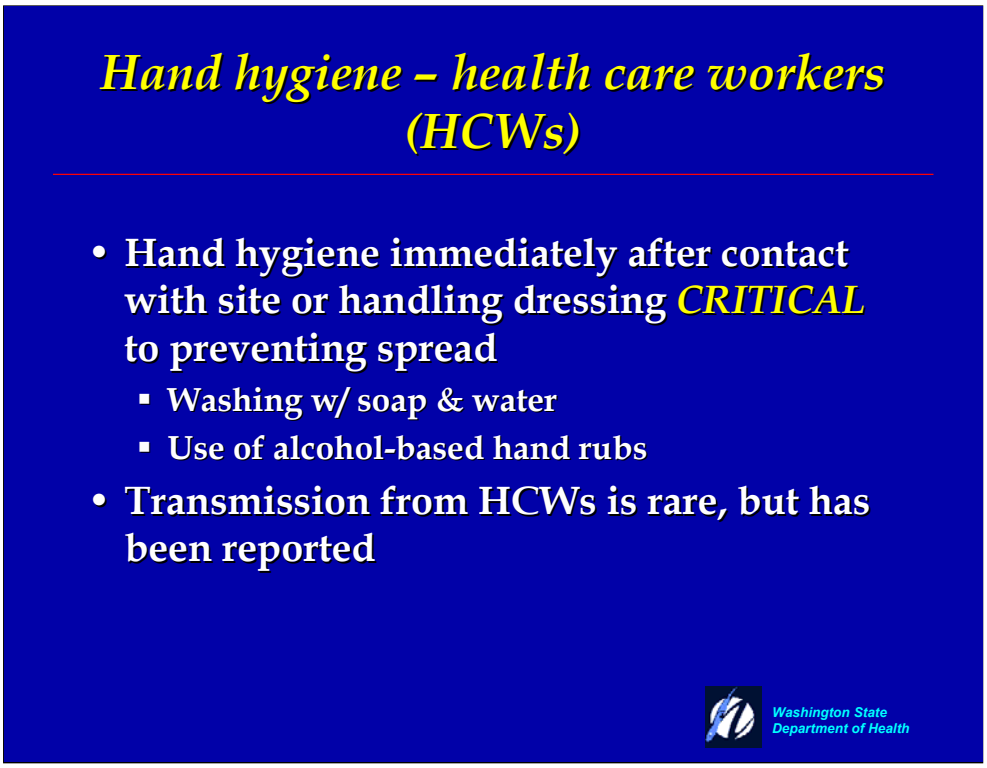
The Advisory Committee on Immunization Practices (ACIP) has specific recommendations for vaccination site care for personnel who have direct patient contact, to decrease the chances of spread of the virus. These workers are advised to use gauze and a single semi-permeable membrane dressing, like Op-site or Tegaderm, over their vaccination site, and to wear clothing over the dressing. The dressing should be worn at all times when providing hands-on patient care.

Vaccinees should have daily, or at least every other day dressing checks while at work, to ensure proper coverage, to reinforce infection control training, and to assess the need for dressing changes, which should occur at least every 3-5 days, or when the dressings become wet.

Vaccination site with gauze & semi-permeable membrane dressing

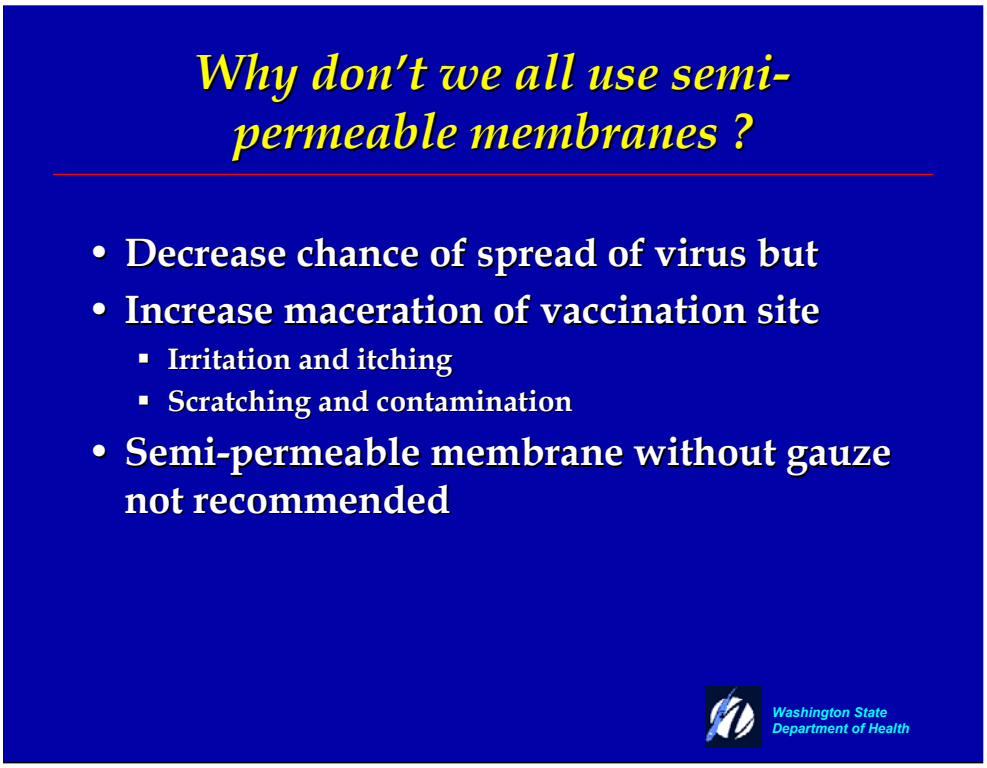


Here's a vaccination site with gauze, covered by a semi-permeable membrane dressing, and incidentally, there's a lot of erythema around the vaccination site, which is normal. This is the dressing recommended for personnel who have direct patient contact.



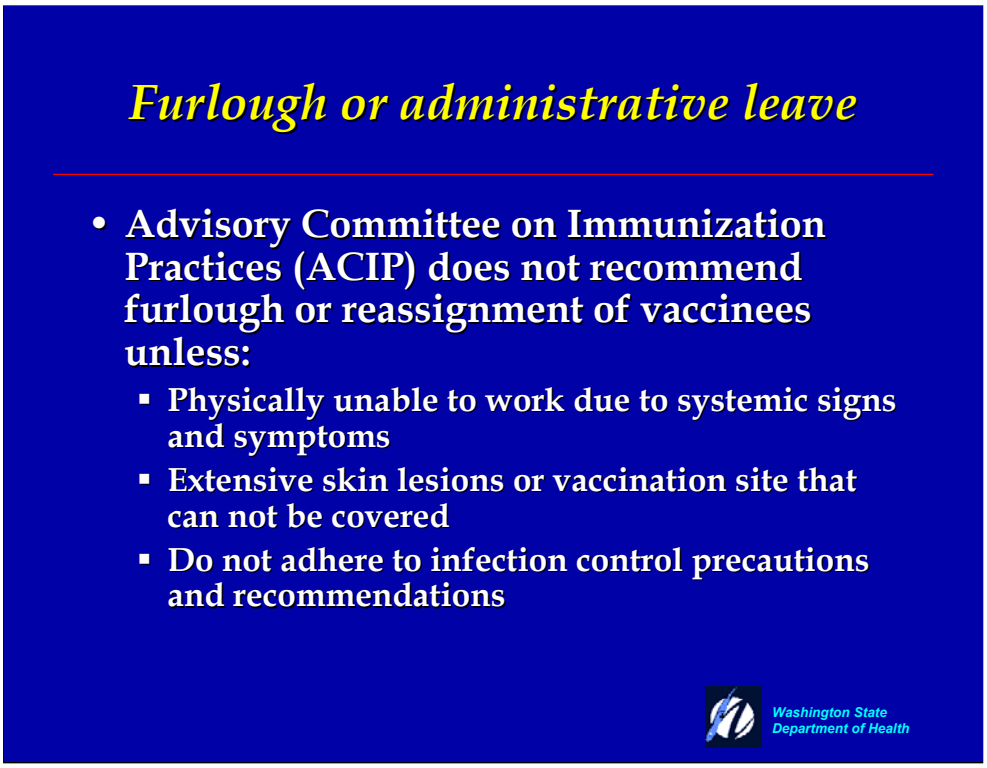
For health care workers – hand hygiene immediately after coming in contact with a vaccine site or handling contaminated dressings is critical to prevent spread of vaccinia, either to another area of their body (inadvertent inoculation) or to close contacts (contact vaccinia). Transmission of vaccinia in a health care setting is rare, but has been reported when smallpox vaccine was given in the past, either routinely or during outbreaks.

Transmission of vaccinia is also a concern in other settings when close personal contact with children or other persons is likely—for example, for parents of infants and young children. In these situations, the vaccination site should be covered with gauze or a similar absorbent material, and a shirt or other clothing should be worn, and careful attention to hand hygiene (hand washing) practiced.



So why don't we all use semi-permeable membranes? Although semi-permeable membranes decrease the chance of spread of vaccine virus, they can also increase maceration of the vaccination site, resulting in prolonged irritation and itching. This in turn can lead to scratching or touching the site, with more opportunity to contaminate the hands.

For this reason, the addition of semi-permeable membranes to dressings is only recommended when someone is engaged in direct patient care. Using a semi-permeable membrane without gauze is definitely not recommended because in recent vaccine trails, this was found to increase irritation and maceration at the site.

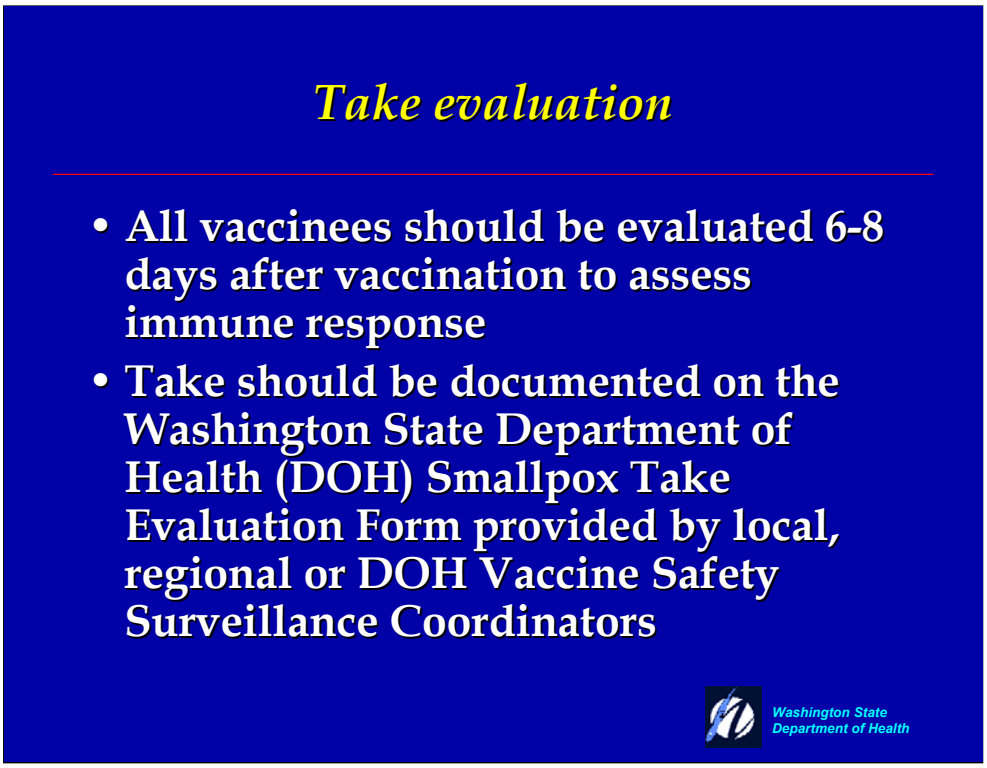


What about furloughing recently vaccinated health car workers? The ACIP does not recommend furlough or reassignment of vaccinees with patient care duties, because they feel that the chances of transmission of virus from health care workers to patients is minimal if proper infection control is observed.

Workers should receive leave if they have symptoms related to their vaccination and are physically unable to work, if they have extensive skin lesions which cannot be adequately covered, or if they don't adhere to the recommended infection control precautions.

It is important to remember that transmission of vaccinia is most likely to occur in households, where prolonged, intimate contact is more likely than in a health care setting.

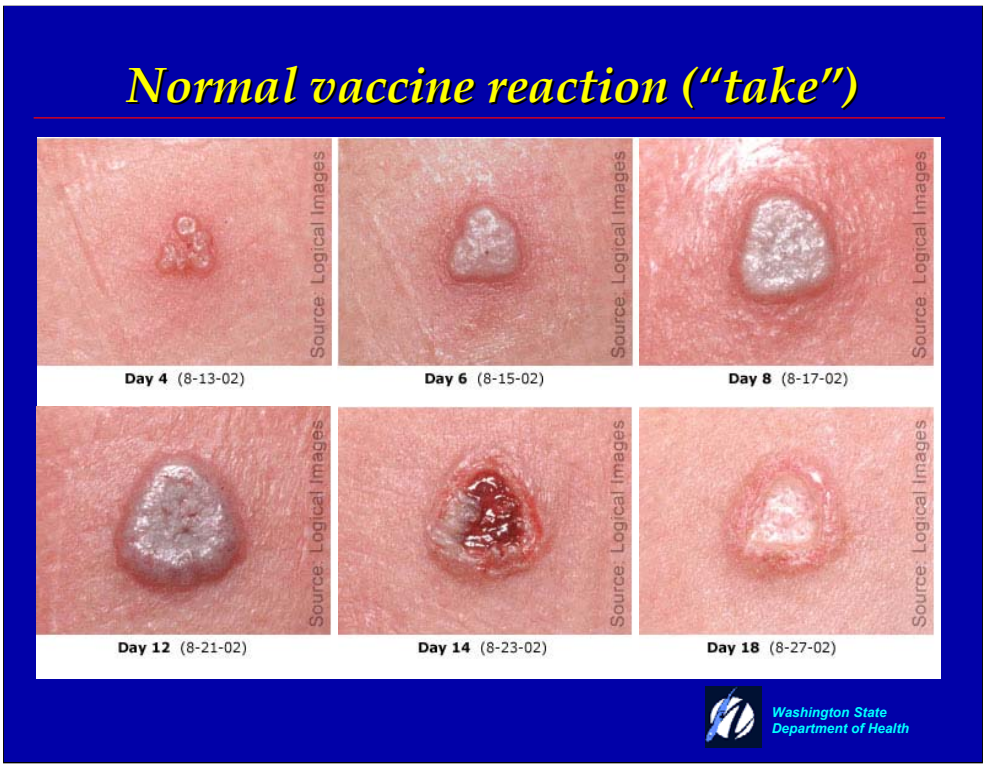
Each institution will need to develop policies regarding the activities of recently vaccinated workers, including those who may be vaccinated at another facility, for example, military reservists.



Following vaccination, all vaccinees should be evaluated at 6-8 days after vaccination to assess their immune response. In the next few slides, I'll describe the assessment of the vaccine reaction, or take, in more detail.

Takes should be documented on the Washington State Department of Health (DOH) Smallpox Take Evaluation Forms which will be provided to all take monitoring sites by their local, regional or DOH Vaccine Safety Surveillance Coordinators. This data will be collected and used to follow-up vaccinees and reschedule those who need revaccination because they did not have a take.

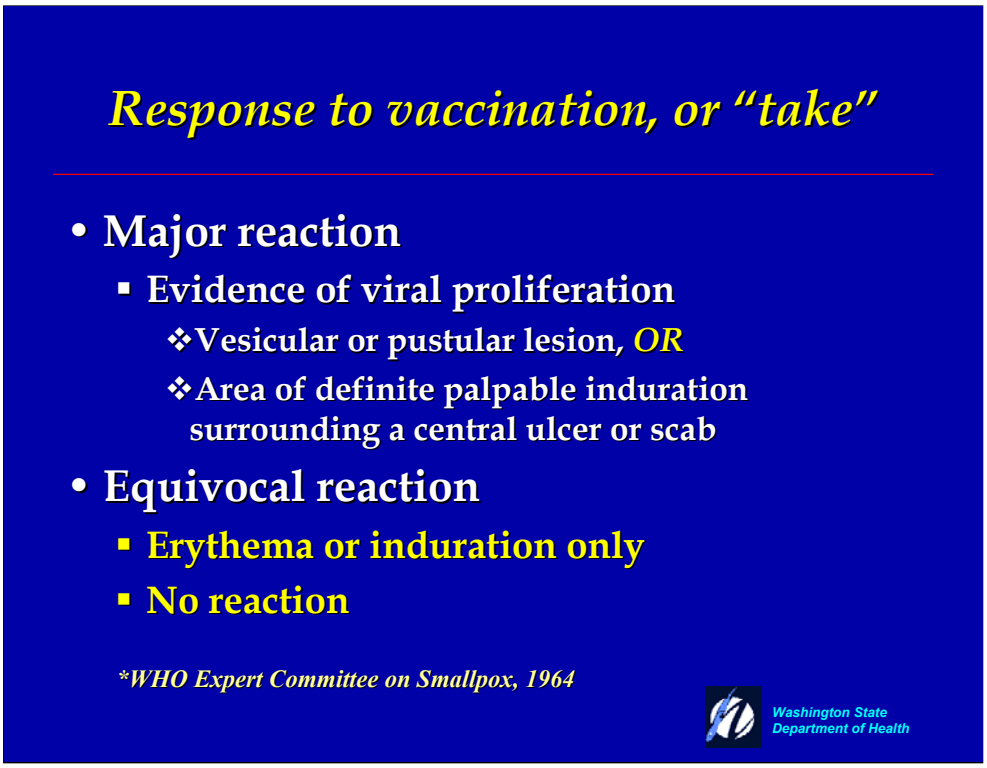
The take should also be recorded on the vaccinees' immunization card. Unsuccessfully vaccinated individuals will be contacted by their local health department to arrange re-vaccination.



This slide shows the normal progression of the vaccination site for an individual who has been vaccinated for the first time ("primary vaccinee"). After inoculation, the virus replicates in the dermis of the skin. By days 2-5, small papules or vesicles will appear, and gradually coalesce, so that by day 6-12, a large pustule is present, surrounded by erythema and induration. The pustule may become dimpled, or umbilicated.

This pustule demonstrates that the vaccination has been successful, and that the vaccinee has a "positive take." Usually by day 14, the pustule begins to dry and crust, forming a scab. The scab will thicken and separate, usually from 3-4 weeks following vaccination, leaving a well-defined scar.

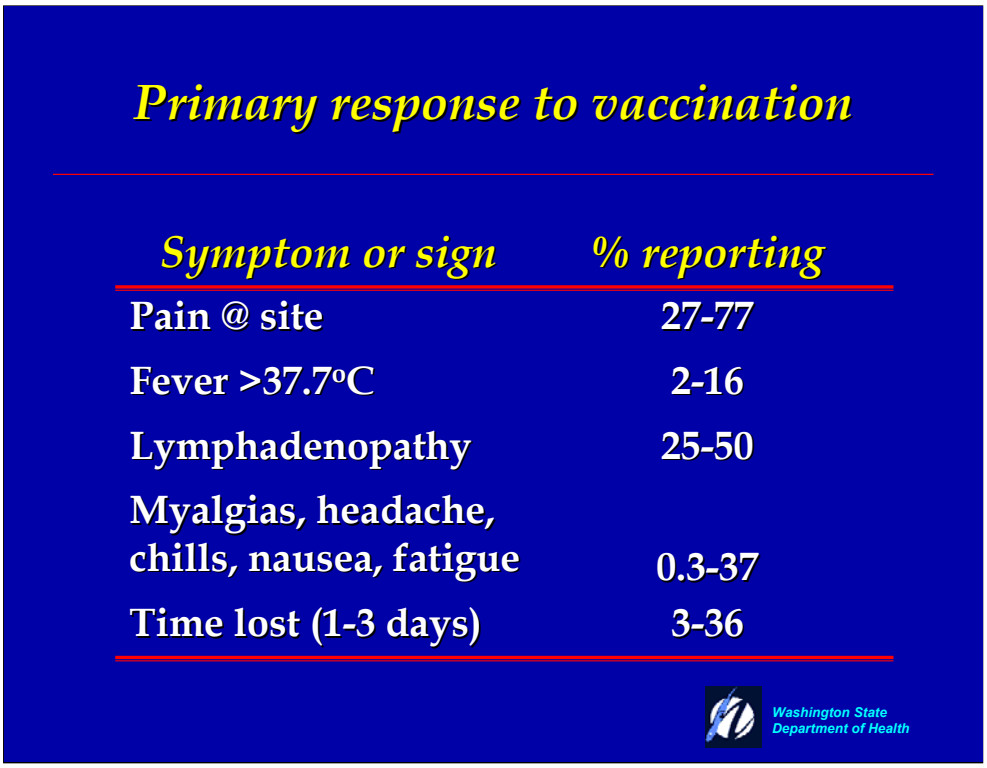
From the time that the vesicles form until the scab separates, the site contains replicating, live virus which can be shed, so that proper site care and infection control are important, particularly for those who have direct patient contact. This can sometimes be difficult, as the site can be intensely pruritic.



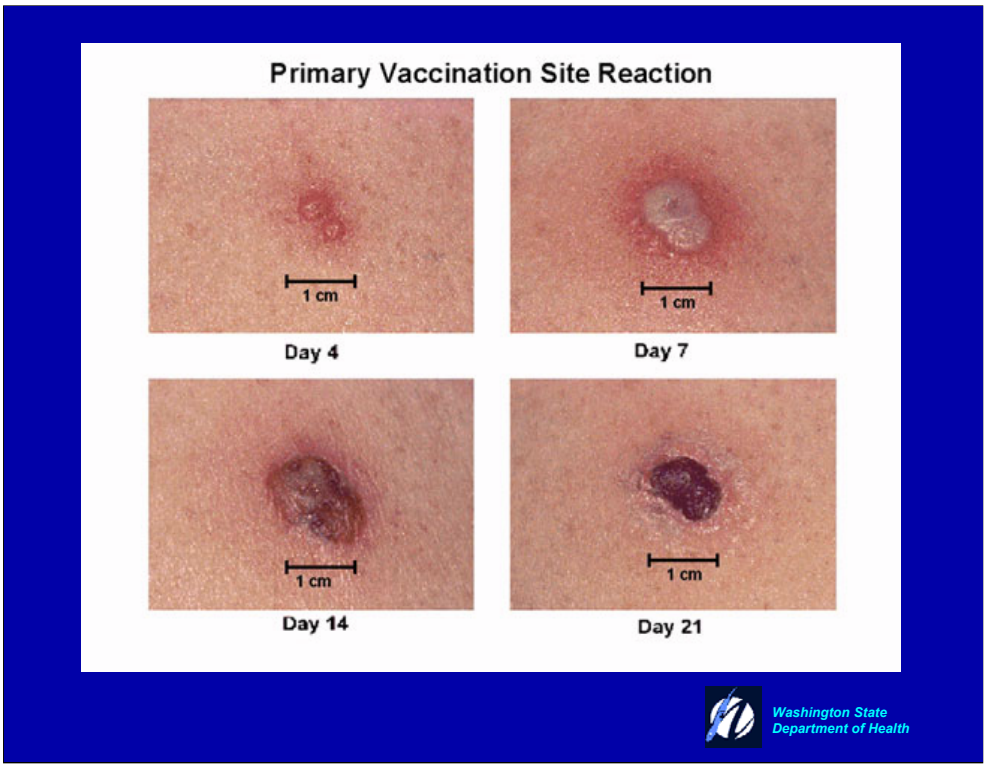
To define successful response to vaccination, or "take," we'll use the criteria established by the World Health Organization Expert Committee on Smallpox in 1964: major and equivocal reactions. Major reactions show clear evidence of viral proliferation: either a formation of a typical vesicular or pustular lesion around the 7th day, or an area of induration surrounding a central ulcer or scab.

An equivocal reaction is anything else – erythema or induration alone, or complete absence of a reaction. Erythema with a small papule that resolves within days of the vaccination is usually a hypersensitivity reaction to the vaccine. Equivocal reactions can occur as a result of residual immunity, poor technique (for example, alcohol used to prep skin, shallow punctures, etc.), or low potency vaccine.

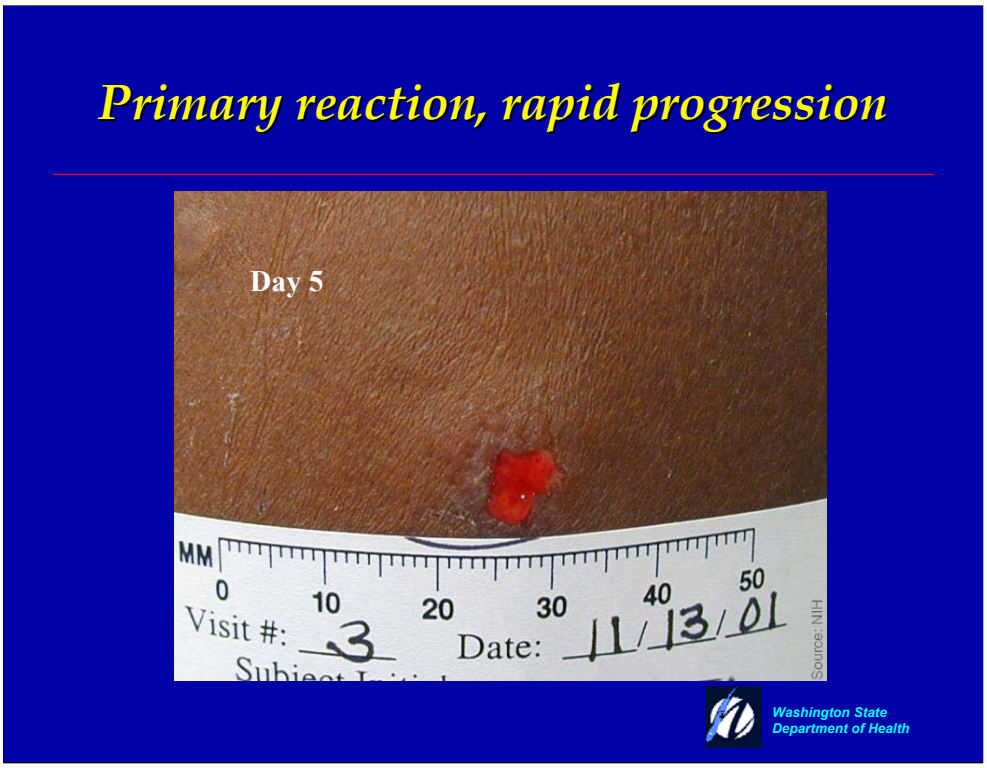
Vaccinees with an equivocal reaction should be considered susceptible and should be revaccinated; if the second attempt is unsuccessful, the vaccination site should be changed for the third attempt. Those who don't respond to three attempts should be considered susceptible to smallpox.



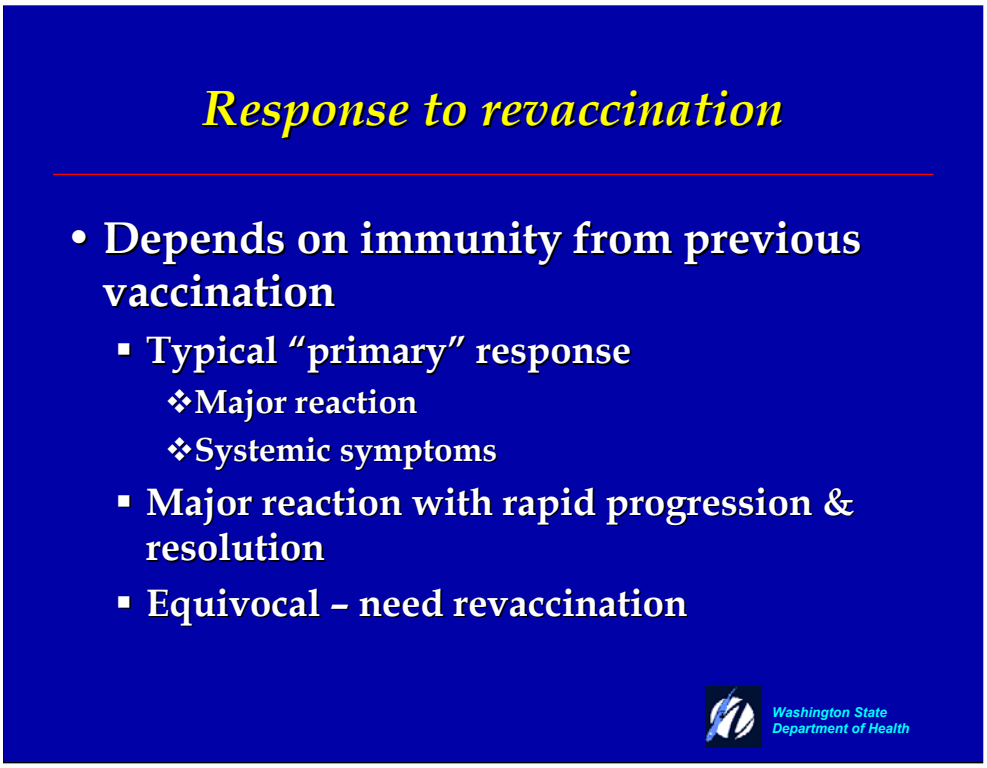
Most people receiving vaccine for the first time will have what is called a primary response with their major reaction - a typical progression from vesicle to pustule to crust over 2-4 weeks, as we saw in the earlier slide. Many will also develop systemic symptoms, which usually coincide with the develop of the pustule, so usually about a week after vaccination. These symptoms are shown on this slide, with the proportion of primary vaccinees reporting them in recent clinical trails sponsored by the National Institutes of Health and the Department of Defense: pain at the vaccination site, with intense erythema and induration; fever; axillary lymphadenopathy; myalgias, headache, chills, nausea, and fatigue. 3-36% of participants took 1-3 days off work, school, recreational activities, or lost sleep due to discomfort related to vaccination. The rate of take among healthy, first time vaccinees is 98-100%.



Here again is the normal progression of primary vaccination, from vesicles on the fourth day to an adherent crust on day 21. It's critical to assess a vaccinee for take at 6-8 days post-vaccination, so a reaction can be correctly interpreted. Some allergic reactions to vaccine proteins may appear as induration with a small vesicle, suggesting a major reaction at day 6, only to fade quickly w/o progression. Some vaccination sites may progress very quickly in persons previously vaccinated, and if evaluated on the 9th day, their take might be missed.

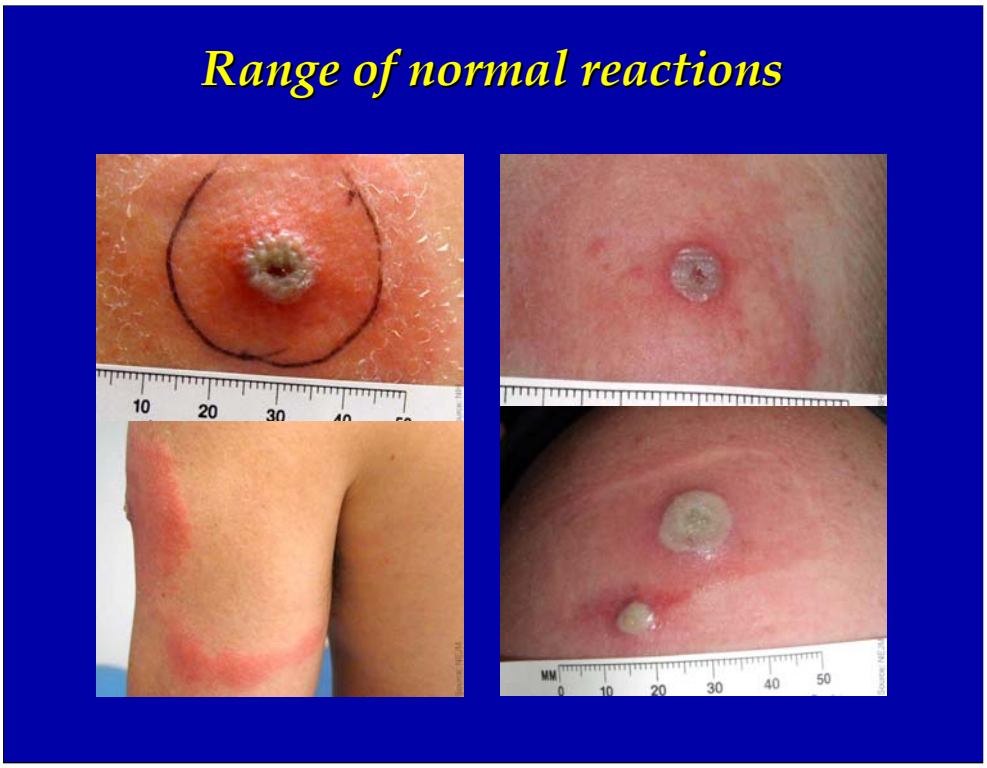


This slide shows a primary reaction with rapid progression in a first time vaccinee -- on the 5th day after vaccination, they have already progressed to a central ulceration surrounded by edema. This is a normal response, with a major reaction.

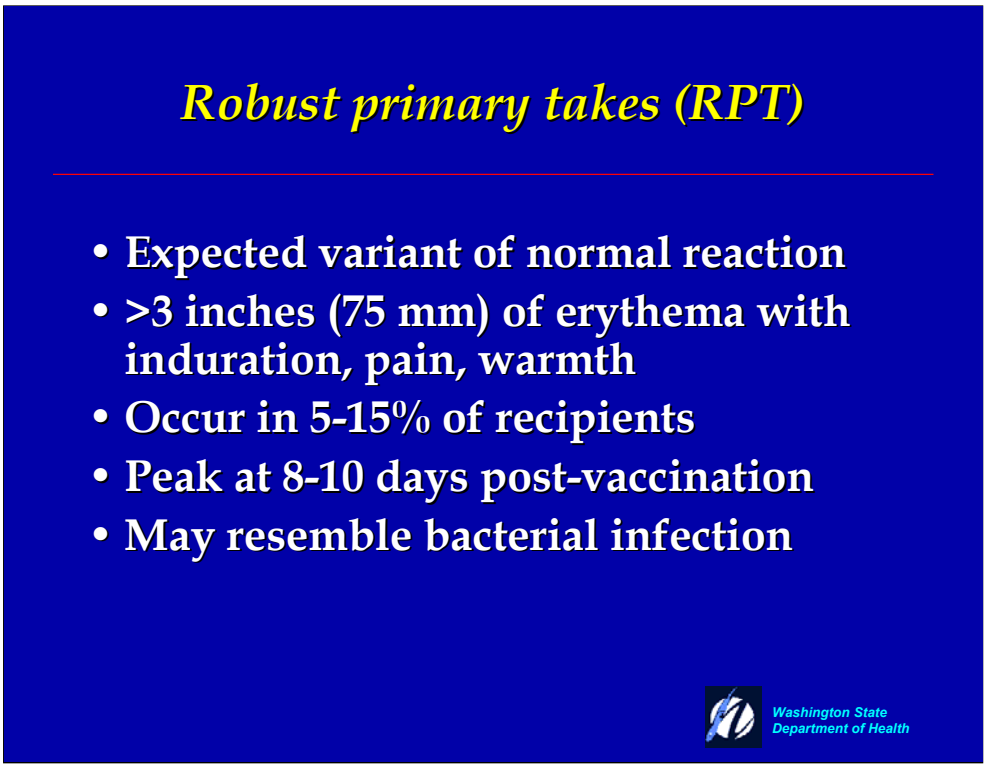


Response to revaccination depends on immunity remaining from previous vaccination. Because most people getting vaccinated now received their last dose of vaccine more than 10 years ago, many will have a typical primary response - a major reaction with some systemic symptoms. More recently vaccinated individuals may have a less vigorous reaction, with fewer systemic symptoms and more rapid progression and resolution of the vaccination site. If the reaction is equivocal, they will need to be revaccinated. The rates of take for revaccination among healthy individuals are 95-98%.

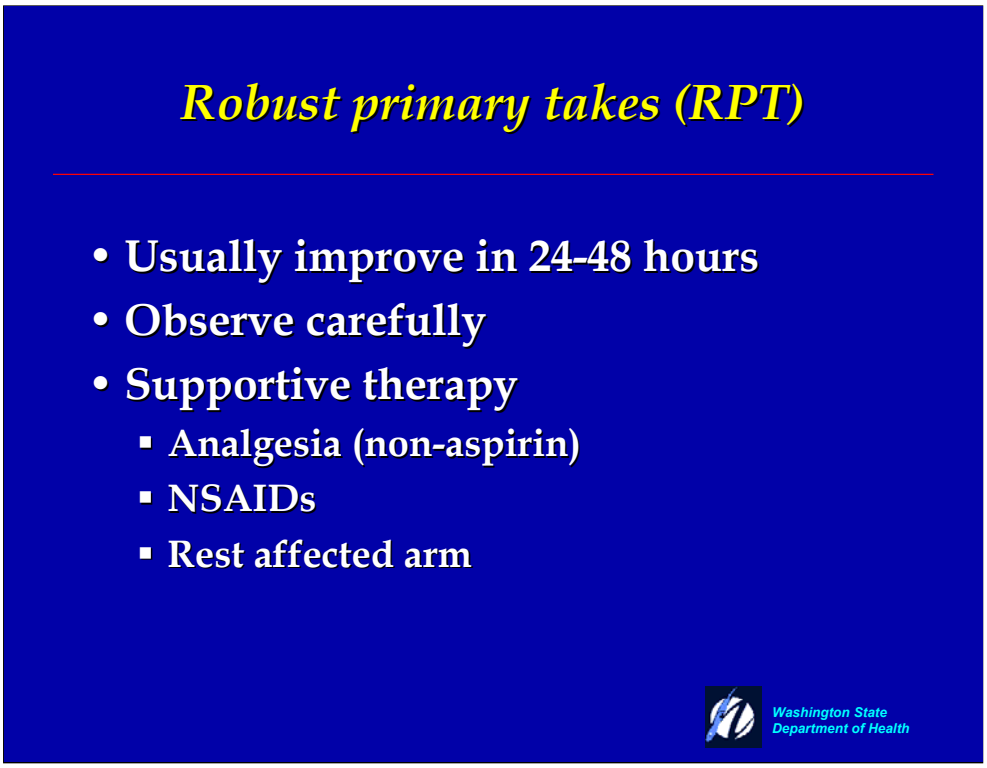
Two images of revaccination – the one on the left shows the well-healed scar of a previous vaccination; the one on the right shows tiny vesicles present on day 3. Both of these are considered normal, and were classified as a major reaction.



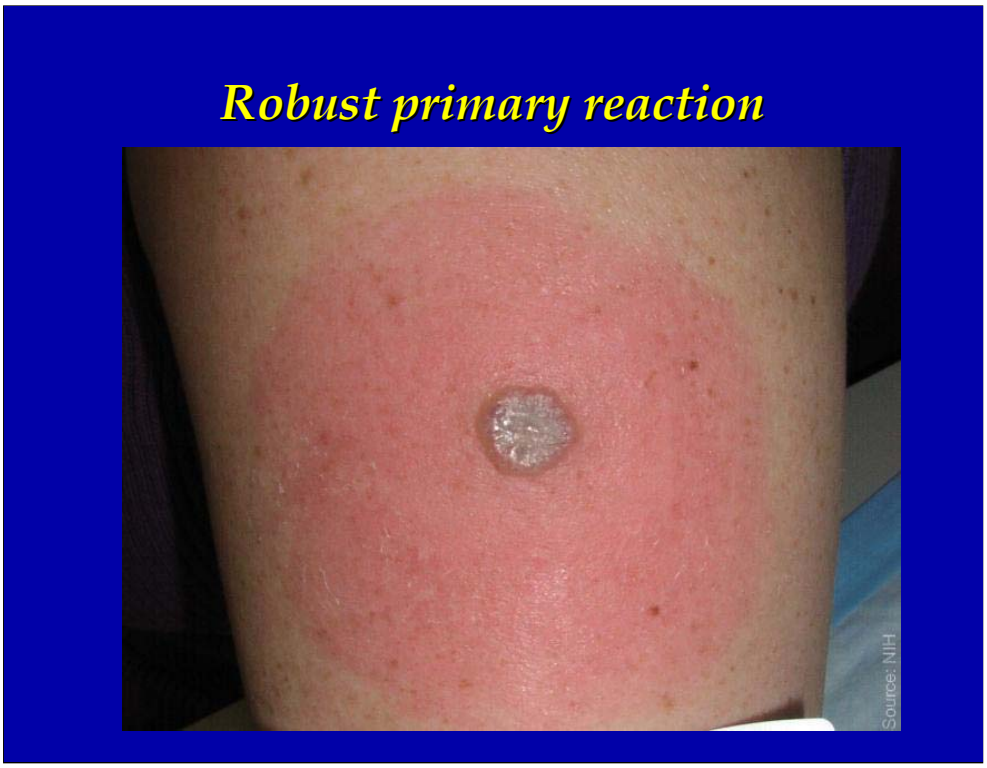
There is a wide range of reactions that are considered normal variants and do not constitute adverse events. These reactions include intense inflammation surrounding the papule or vesicle (also known as “viral cellulitis”) with intense induration and local edema, lymphangitis, lymphadenopathy, all of which are normal and sometimes referred to as a “robust primary take.” The development of adjacent satellite lesions may also occur. Despite their sometimes alarming appearance, these reactions do not require more than symptomatic treatment.



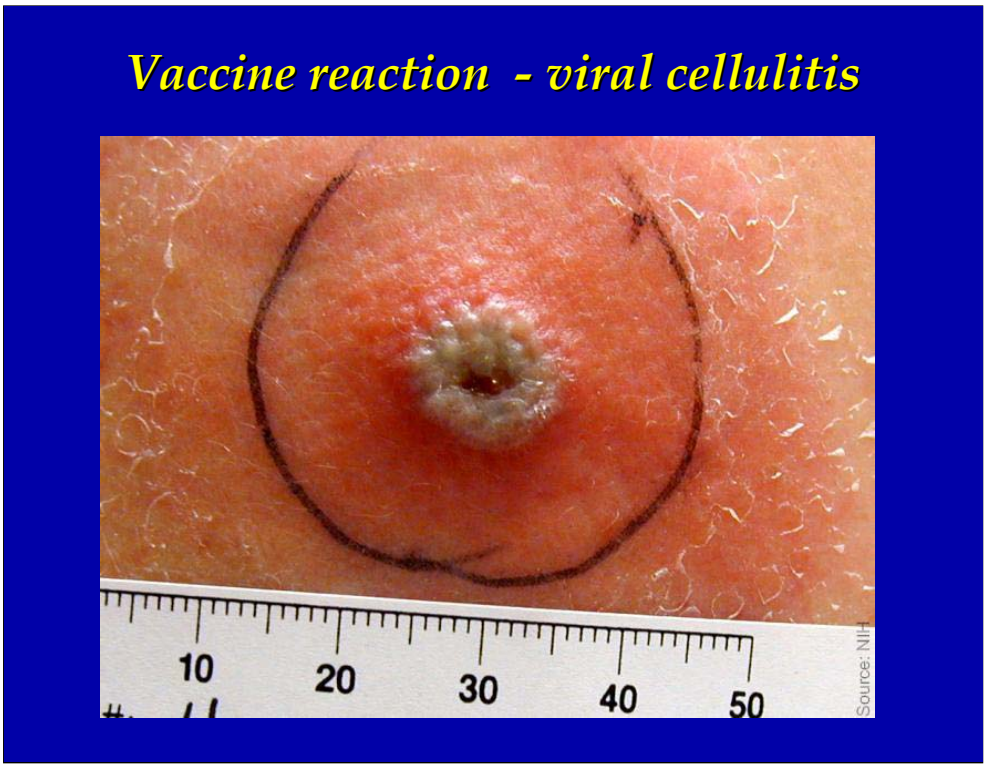
Robust primary takes (RPT) are most commonly seen in people being vaccinated for the first time, or with revaccinees who were previously vaccinated more than 10 years ago, which will be most of the people we vaccinate in this program. RPTs are an expected variant of normal vaccination reactions, and are defined as a vaccination site that has >3 inches (>75 mm) of erythema and induration. RPTs occur in 5-15% of vaccine recipients, and peak at 8-10 days after vaccination. RPTs can appear alarming to both the vaccinees and those providing follow-up care, as they may resemble a bacterial infection.



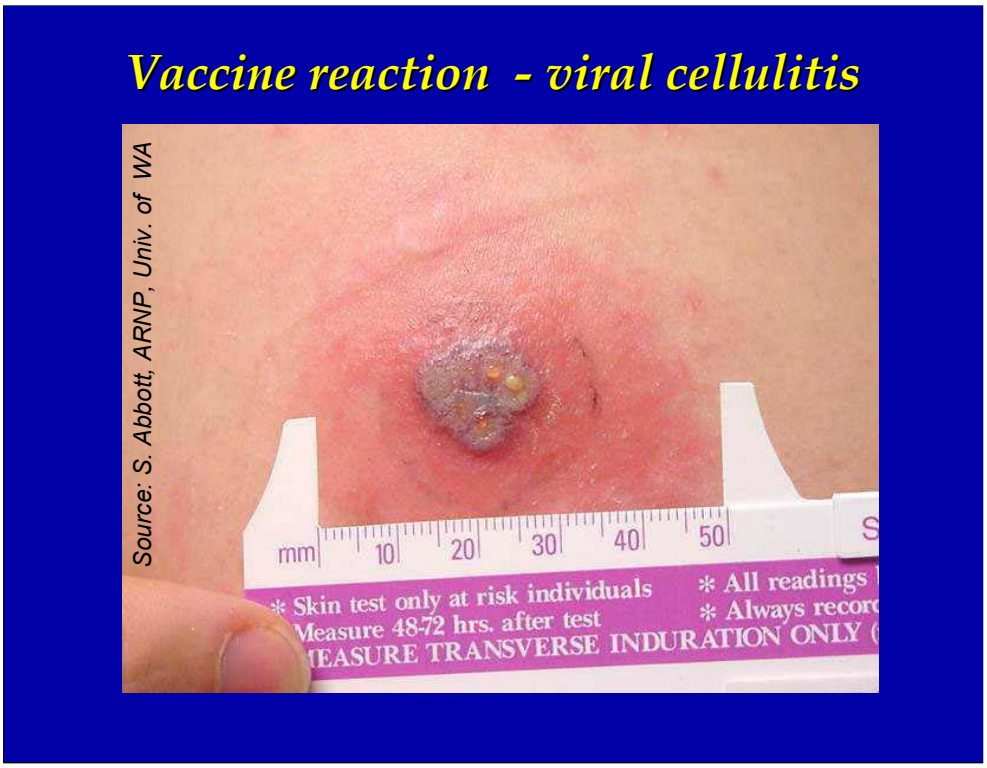
Robust primary takes (RPTs) usually improve in 24-48 hours, but should be observed carefully. If uncomfortable, vaccinees can be treated symptomatically with acetaminophen, non-steroidal anti-inflammatories, and by resting the affected arm.



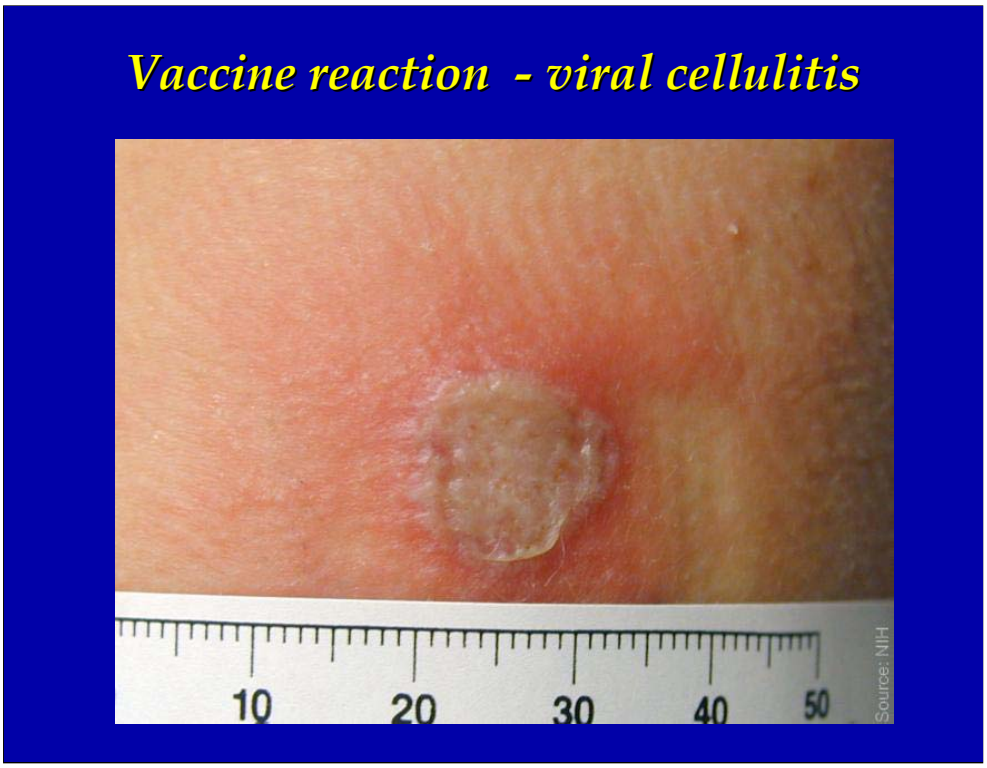
A healthy, first time vaccinee with a robust primary take, a large area of erythema and induration surrounding their vesicle.



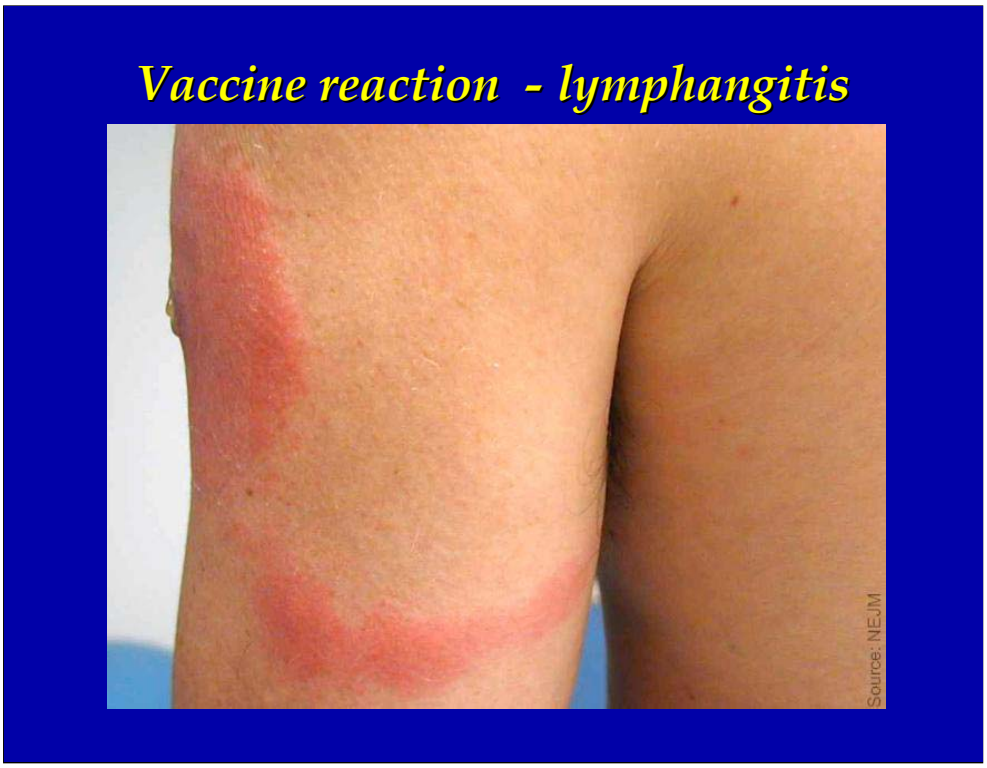
The next few slides show viral cellulitis, a normal response that may prompt clinicians unfamiliar with the range of normal vaccination responses to treat the vaccinee unnecessarily with antibiotics. Viral cellulitis and pronounced local edema are normal, although exuberant reactions, more common in primary vaccinees – it is important to distinguish this from bacterial cellulitis, which is a true adverse event requiring specific treatment. I will discuss bacterial infection later in the section on adverse events.



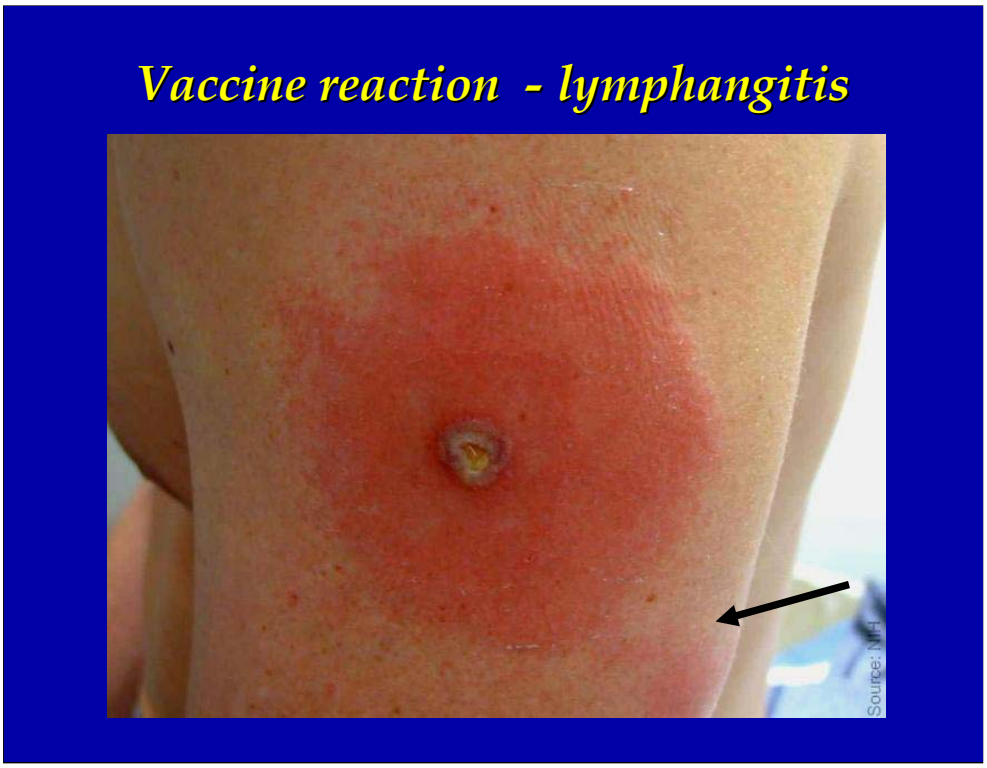
Viral cellulitis



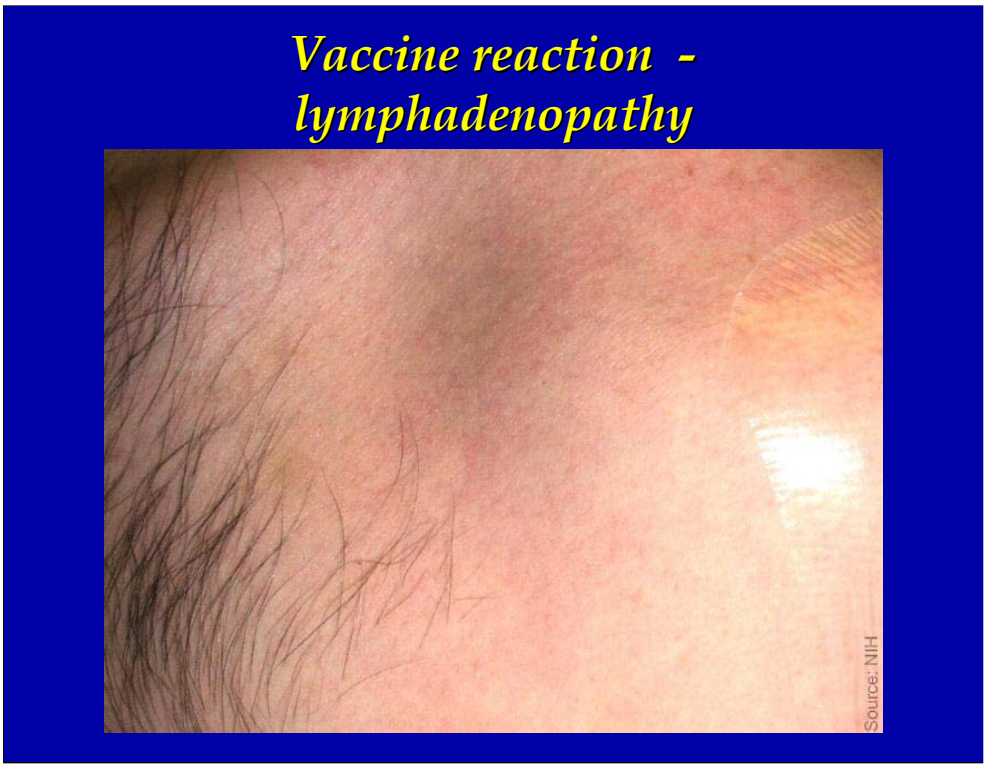
Viral cellulitis with local edema.



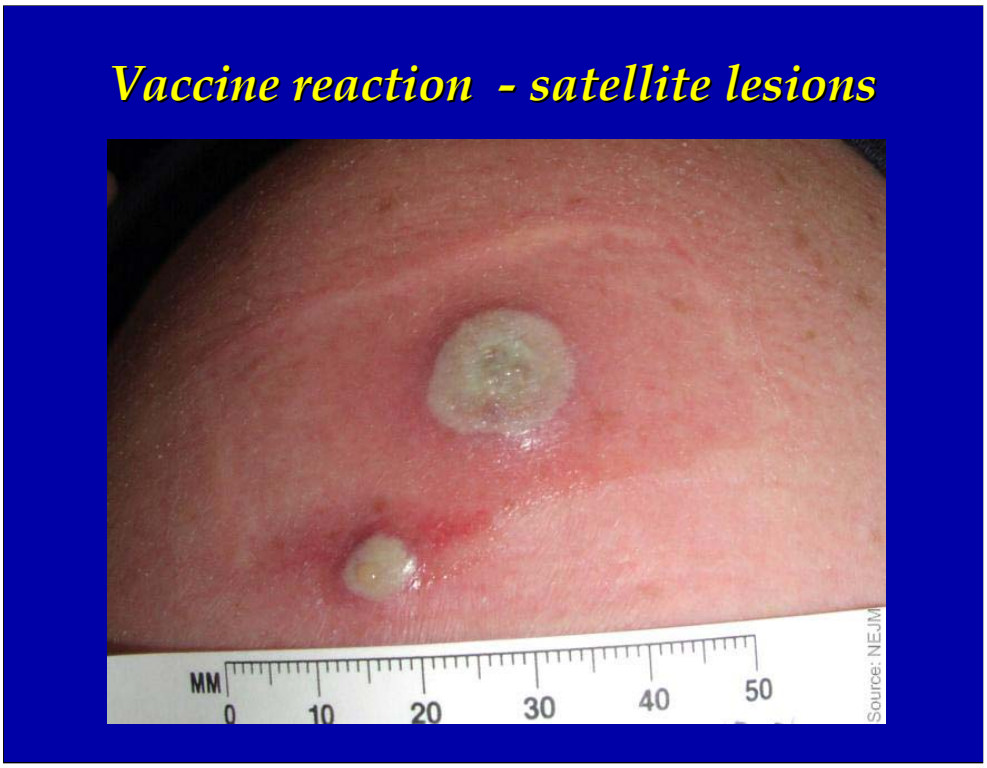
Lymphangitis can occur as a normal reaction to viral replication at the site of the vaccination, and may spread from the site. This is another reaction that may appear alarming, particularly in combination with viral cellulitis, and could lead to unnecessary use of antibiotic therapy. This is a normal reaction in a primary vaccinee.



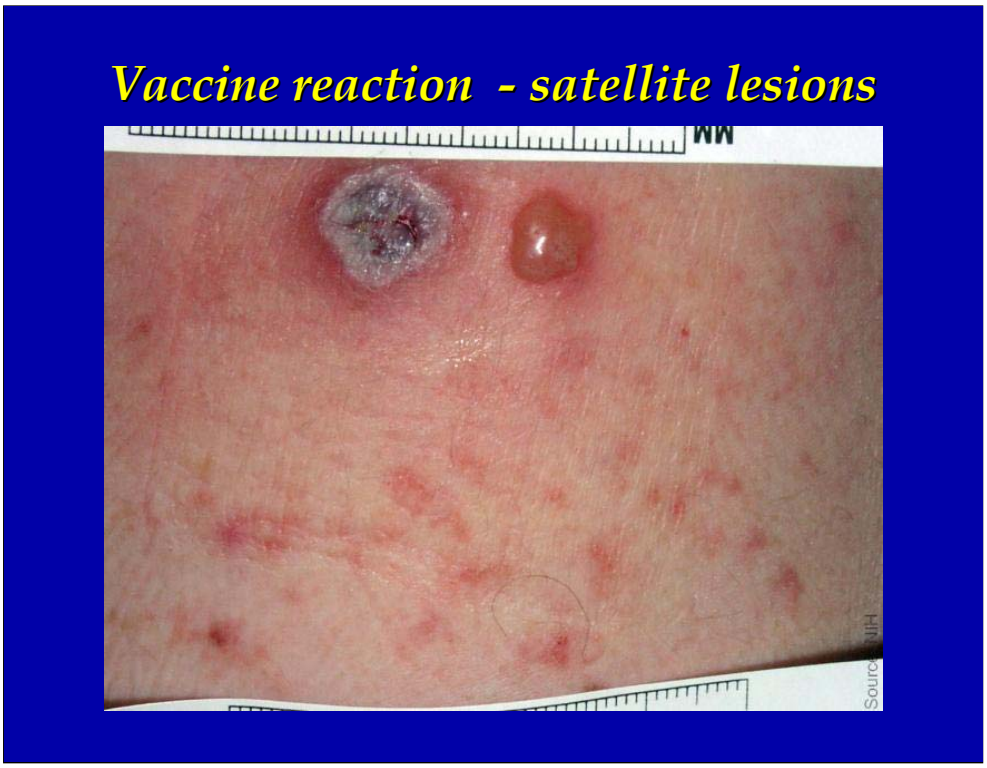
This vaccinee has a robust primary take with lymphangitis indicated by the arrow at the lower right hand of the picture. Again, a normal reaction to vaccination.



Axillary lymphadenopathy is common (25-50%), usually appears 3-10 days following vaccination, and may persist for up to 2-4 weeks after the vaccination site has healed. This slide shows an unusual reaction – this man has infraclavicular lymphadenopathy on the same side as the vaccination site – seen in the middle of the slide between the chest hair and the semi-permeable membrane at the right hand side of slide.

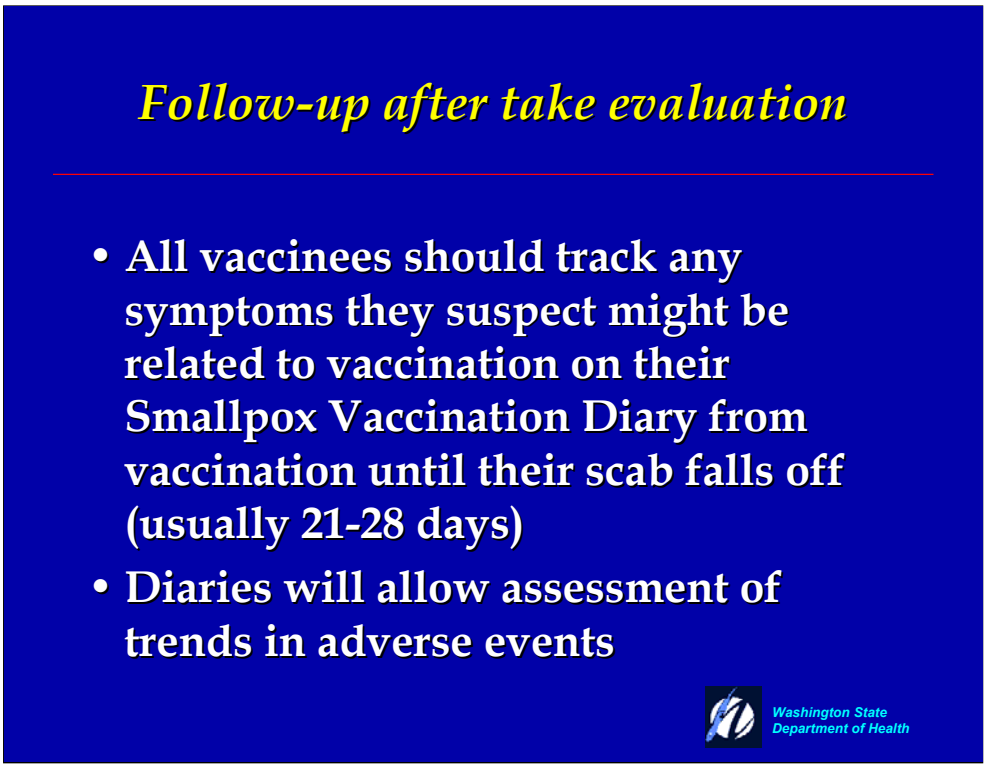


Satellite lesions may occur in 3-7% of vaccinees. These are also normal, and require no specific treatment, but care should be taken to make sure that dressing covers all lesions that result from vaccination. The next few slides show examples of satellite lesions.



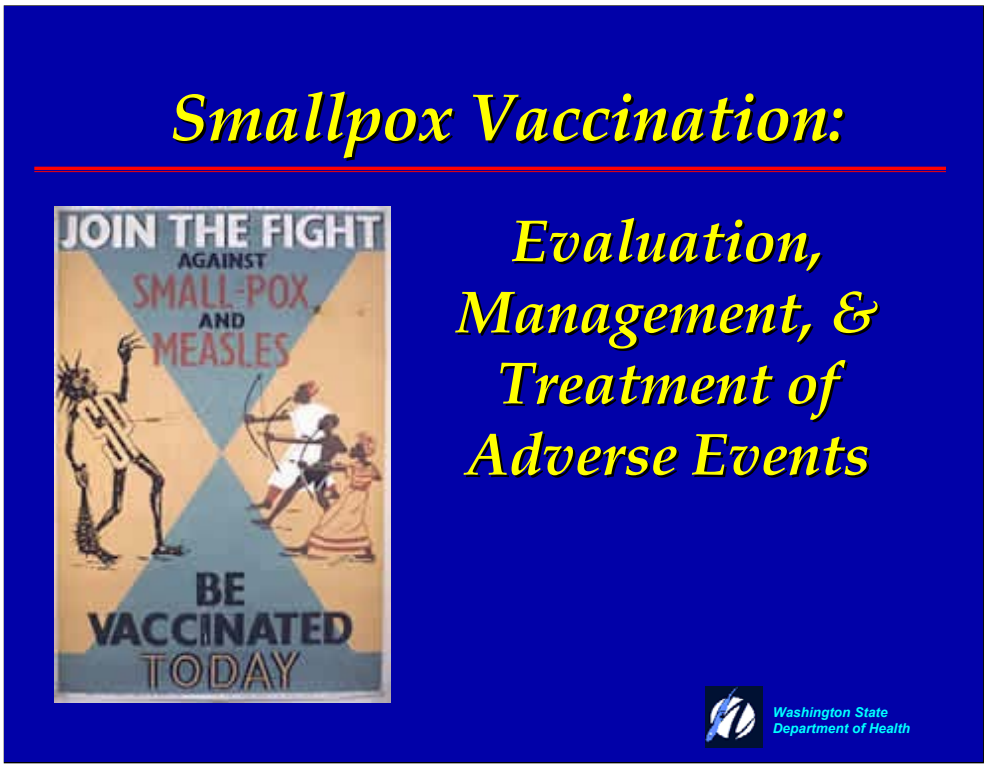
Small and large satellites – not always in the same stage as the vaccination site.

Large, robust primary take with edema, satellite lesions, and a necrotic appearing central ulceration – normal reaction in a healthy child that did not require antibiotic treatment.

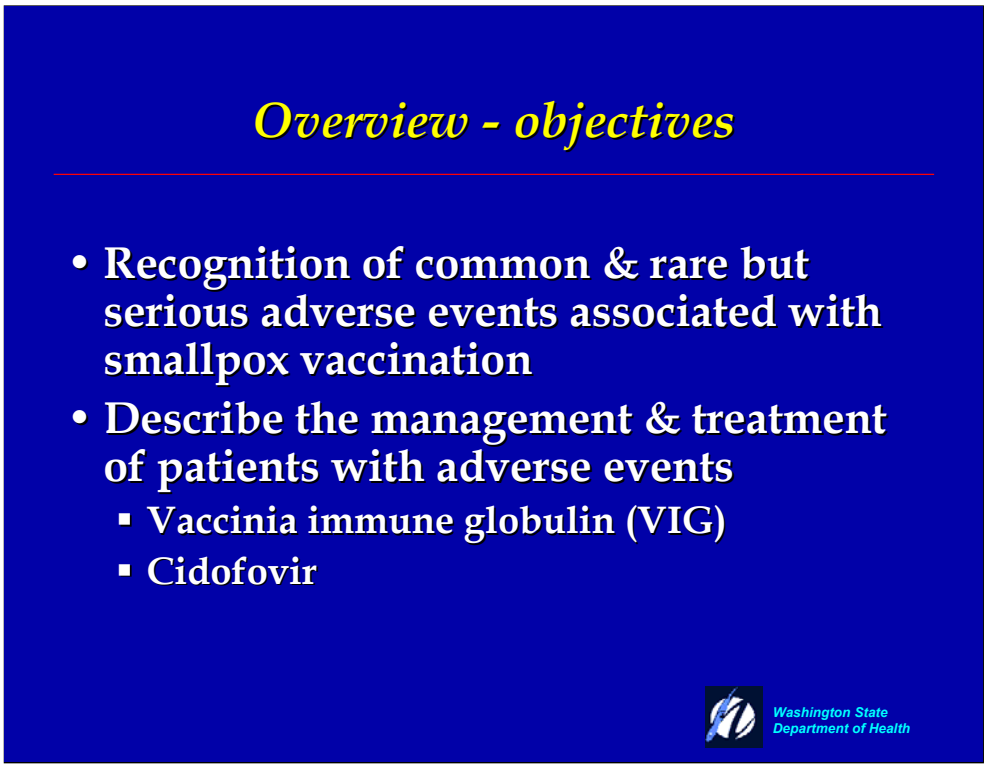


Follow-up after take evaluation is also important. All vaccinees should track any symptoms that they suspect might be related to their vaccination on their Smallpox Vaccination Diary from the time they are vaccinated until their scab falls off – usually from 21-28 days. These diaries ask the vaccinee to record symptoms like fever, tender lymph nodes, headache, difficulty sleeping, or work or activities missed due to vaccine reaction.

The data from these diaries will allow us to assess how the smallpox vaccination program is going in WA – and help us to identify any trends in minor adverse events. Vaccinees will be given instructions at the time of vaccination on how and where to submit their diaries.

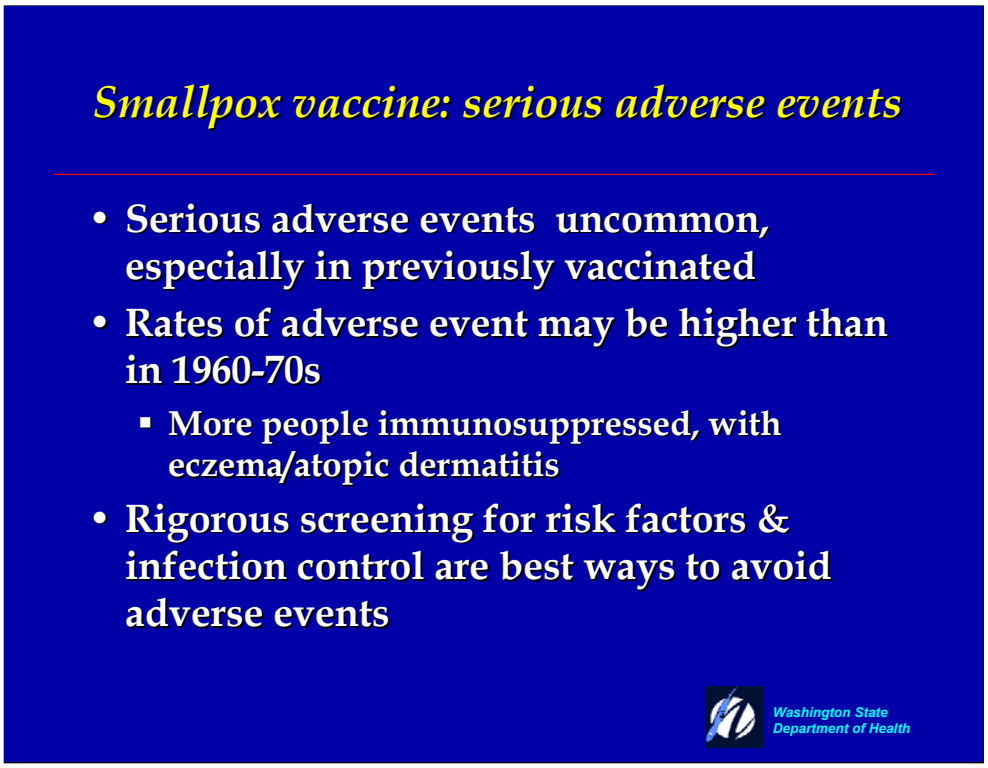


So after seeing normal reactions to vaccination, now we'll spend some time reviewing both common and rare adverse events that might be expected following smallpox vaccination



This portion of the talk will focus on the recognition of common and rare but serious adverse events associated with smallpox vaccination, and will describe the management and treatment of patients with adverse events.

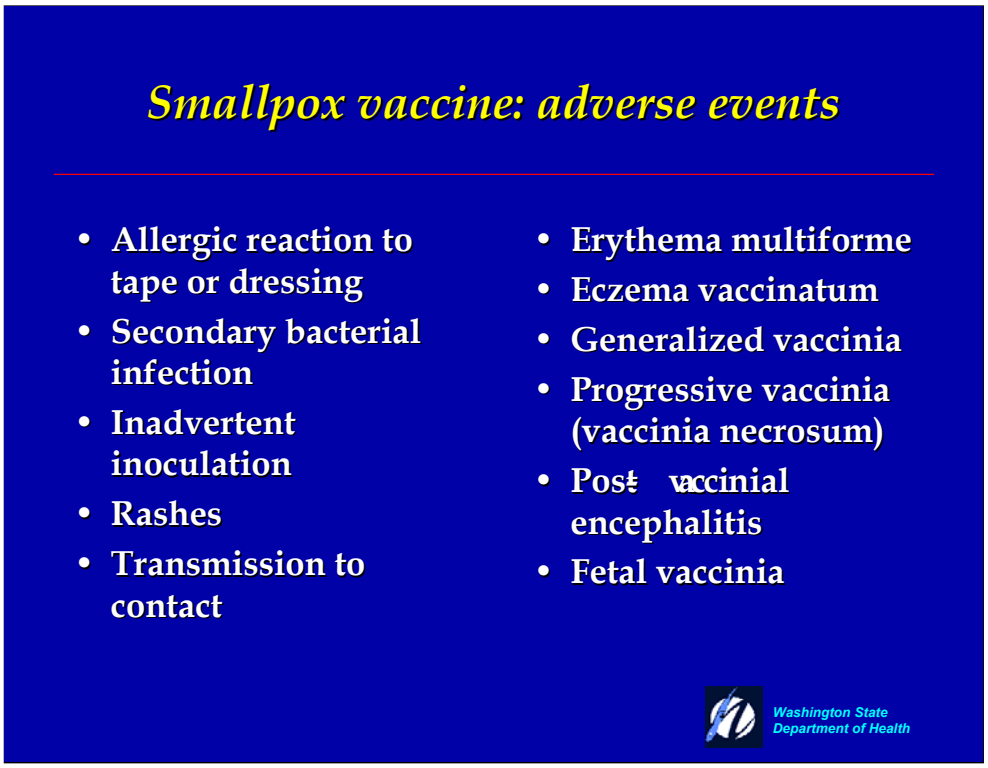
I will also discuss the use of specific treatment for adverse events – vaccinia immune globulin, or VIG and, the antiviral agent cidofovir, which is considered second line therapy. Both are available from the Centers for Disease Control and Prevention (CDC) under an Investigation New Drug, or IND protocol. Finally, I will give you information about how to obtain clinical consultation for patients with suspected adverse events, how to obtain VIG and cidofovir under IND protocol, and how to report adverse events associated with smallpox vaccination.



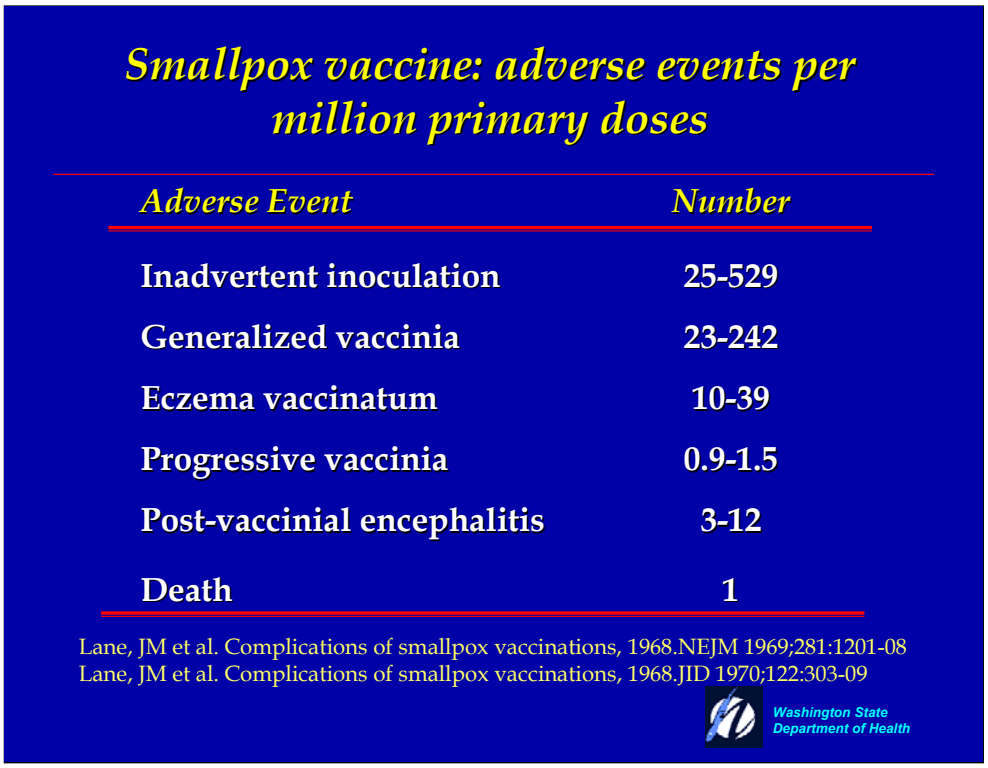
In general, serious adverse events are uncommon, especially among previously vaccinated individuals. However, the rates of adverse events may be higher today than in the 1960 & 70s when vaccine was given routinely, for several reasons. There are now more people at risk for adverse events, and fewer people who are immune to vaccinia, because we no longer routinely vaccinate.

More people are now immunosuppressed due to HIV infection, cancer therapy or stem cell or organ transplants. In addition there is some evidence that the rates of eczema and atopic dermatitis have increased since 1970.

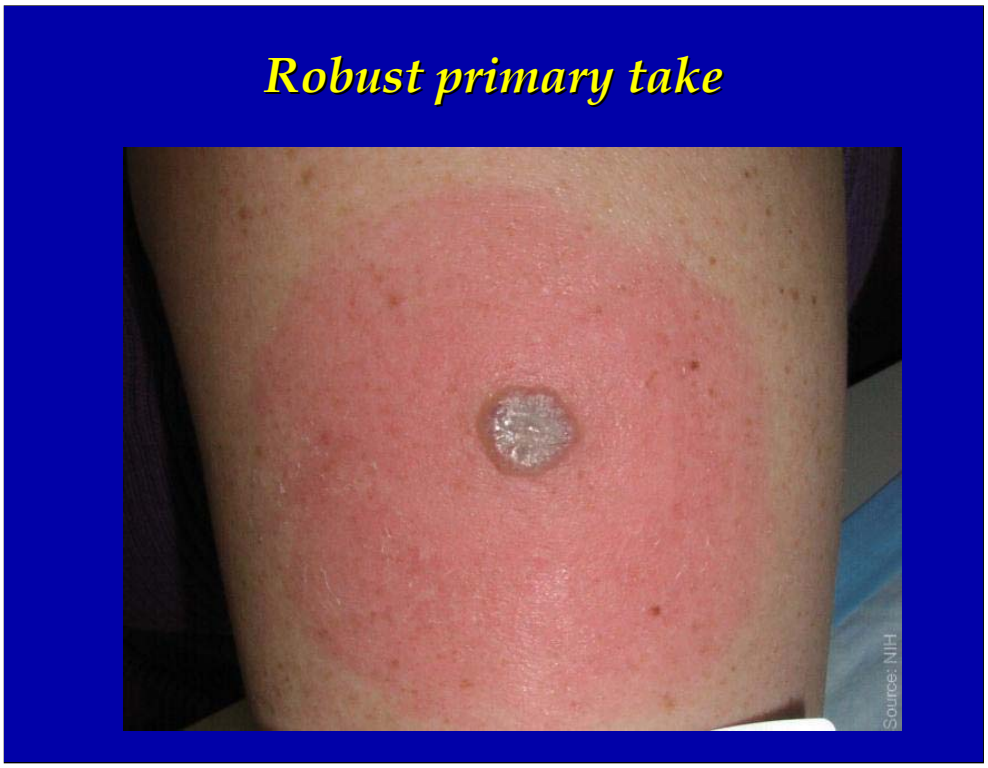
Rigorous screening of potential vaccinees for risk factors and the prevention of secondary vaccinia through infection control are the best ways to avoid adverse events. In addition, because as much as 20% of adverse events occur among susceptible contacts of vaccinees, intimate and household contacts should also be screened for conditions that would put them at risk for adverse events if they contracted secondary vaccinia.



Here's a list of all things that can go wrong – from allergic reactions to tape or dressing, to rashes, to very serious and life-threatening adverse events like eczema vaccinatum, progressive vaccinia and post-vaccinial encephalitis. I will discuss the recognition and management of these adverse events in detail.

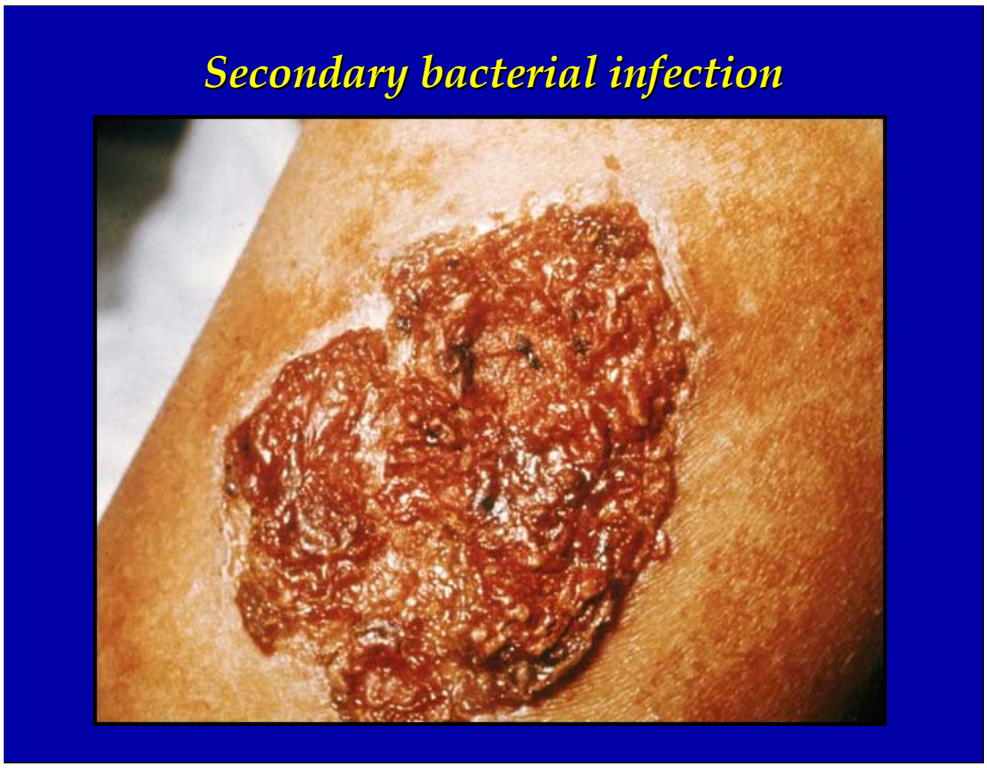


This table shows the range of rates of adverse events seen among first time, or primary vaccinees during the late 1960s. The numbers represent the rate per million doses of vaccine. Of note, the most common adverse event is inadvertent, or accidental inoculation, followed by generalized vaccinia. Fortunately, the more serious adverse events are less common, but it's been estimated that from 15-40 primary vaccinees per million will have a life-threatening adverse event after smallpox vaccination.

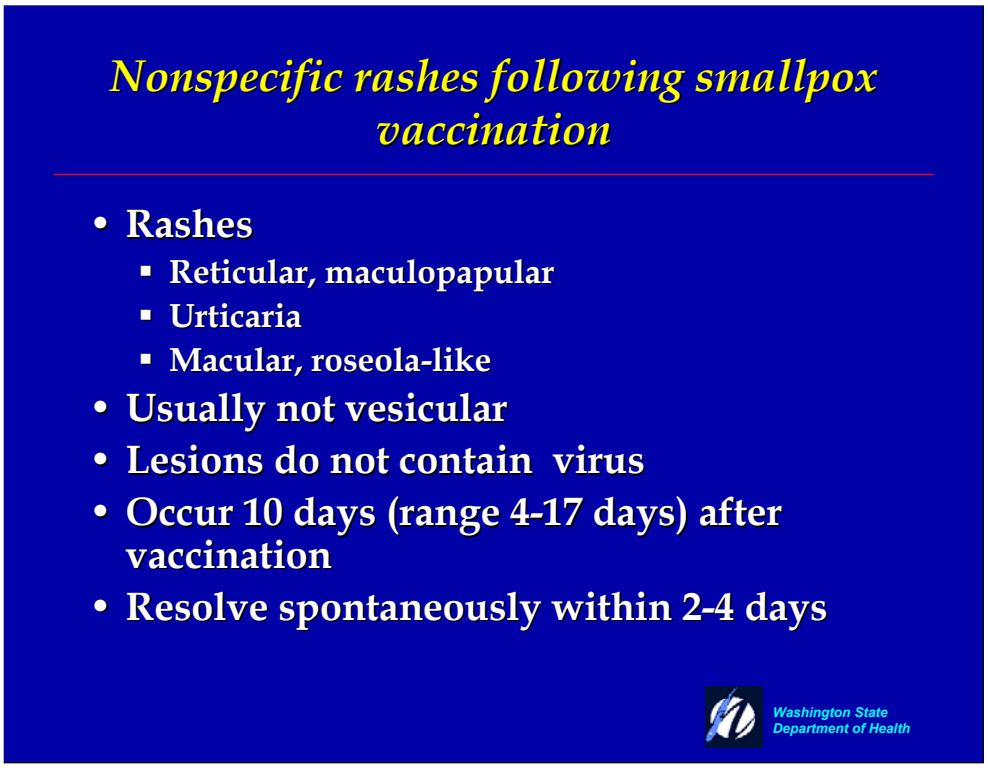


Here's our normal, robust primary take again, with lots of induration and erythema surrounding the central pustule at about day 7. Two local reactions which may be difficult to distinguish from a robust primary take include allergic reactions to tape or dressing, and secondary bacterial infections.

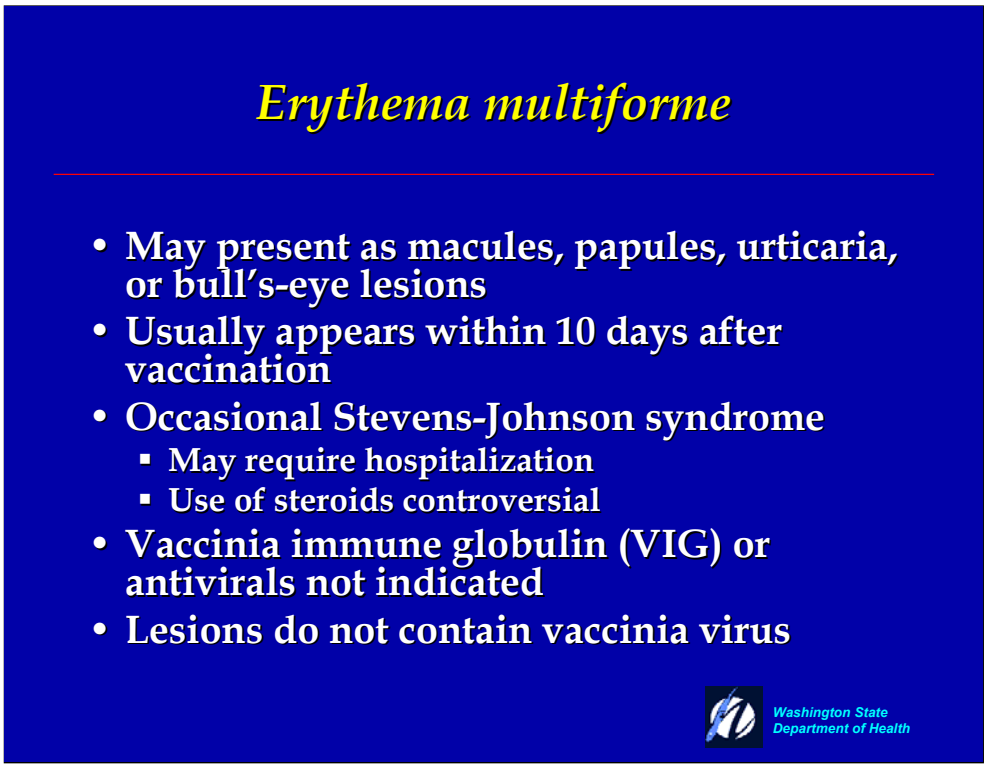
Here's an individual who had an allergic reaction to a semi-permeable dressing – note normal central vesicle,surrounded by a pale halo – this is the area that was covered by gauze, and the rest of the arm is erythematous and intensely itchy where a semi-permeable membrane touched the skin. Distinguishing an allergic reaction from a robust primary take can be a challenge – but usually with an allergic reaction, the area of inflammation corresponds to the pattern of the dressing or the tape used. In addition, unlike a robust primary take, the affected arm is usually not tender, and systemic symptoms are absent. Treatment involves switching to an alternative dressing or hypo-allergenic tape, and antihistamines. Topical or oral steroids should be avoided.



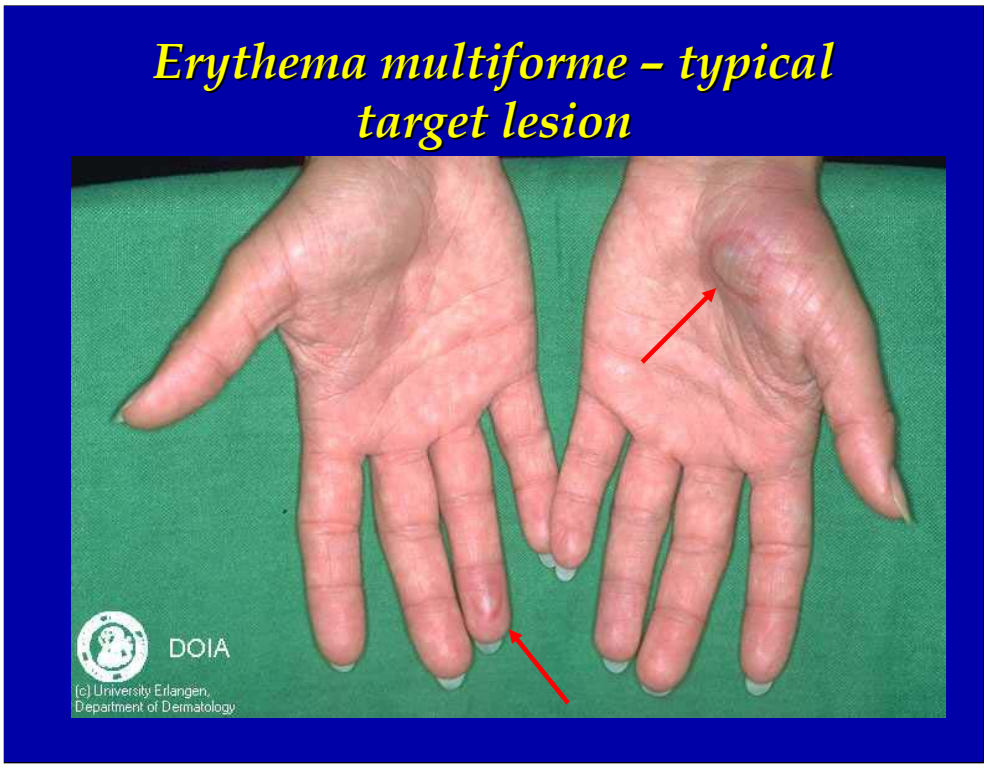
Here's a slide of a patient with a secondary bacterial infections of their vaccination site. Unfortunately, not all are this dramatic or obvious, and an early bacterial infection may be difficult to distinguish from a robust primary take, especially if there is accompanying lymphangitis. Bacterial infections are more common in children than adults, and were more common when thigh and lower back sites were used for vaccination. Staph. aureus and Strep. pyogenes are the most common pathogens, but mixed aerobic and anaerobic infections may occur. Patients may become serious ill, with bacteremia and extensive soft tissue involvement, and necrotizing fasciitis following vaccination has been described. Fortunately, bacterial infections were rare even in developing countries under poor hygienic conditions. In the US in 1963, only 2 bacterial infections were reported among 14 million vaccinations. In general, robust primary takes improve without treatment within 24-48 hours, while cellulitis would continue to progress. Diagnosis can be confirmed by Gram stain and culture, with the results of culture guiding antimicrobial therapy.



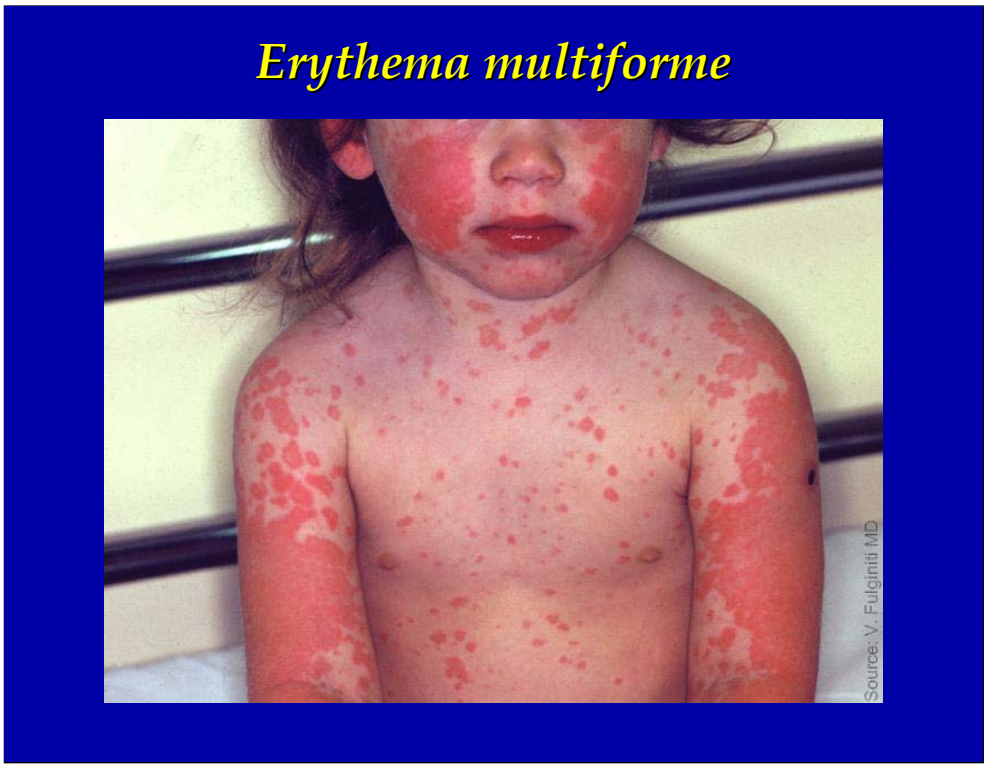
Nonspecific rashes can develop following vaccination – these rashes may be adjacent or distal to the vaccination site, and include reticular, maculopapular rashes, urticaria, and a flat, broad, macular roseola-like rash. These rashes rarely become vesicular, do not contain virus and do not result from viral dissemination. The rashes usually occur about 10 days after vaccination and resolve spontaneously within 2-4 days.



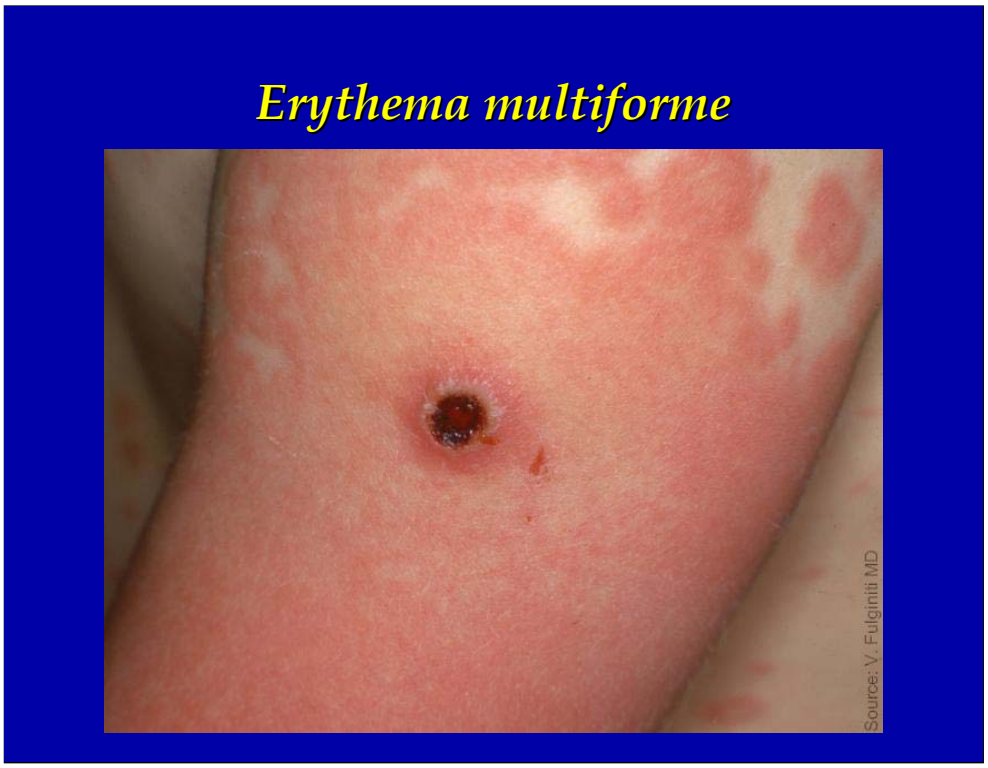
Erythema multiforme is the most common rash that develops after vaccination. The rash may be macular, papular, urticarial, or appear as classic "bull's eye" lesions. It may occur locally, or be generalized. EM usually appears within 10 days following vaccination and is probably immune-mediated. Severe EM is also known as Stevens-Johnson syndrome, which may require hospitalization for hydration and skin care. EM or SJS do not respond to treatment with vaccinia immune globulin (VIG), or antivirals. The lesions do not contain virus, therefore contact precautions are not indicated.



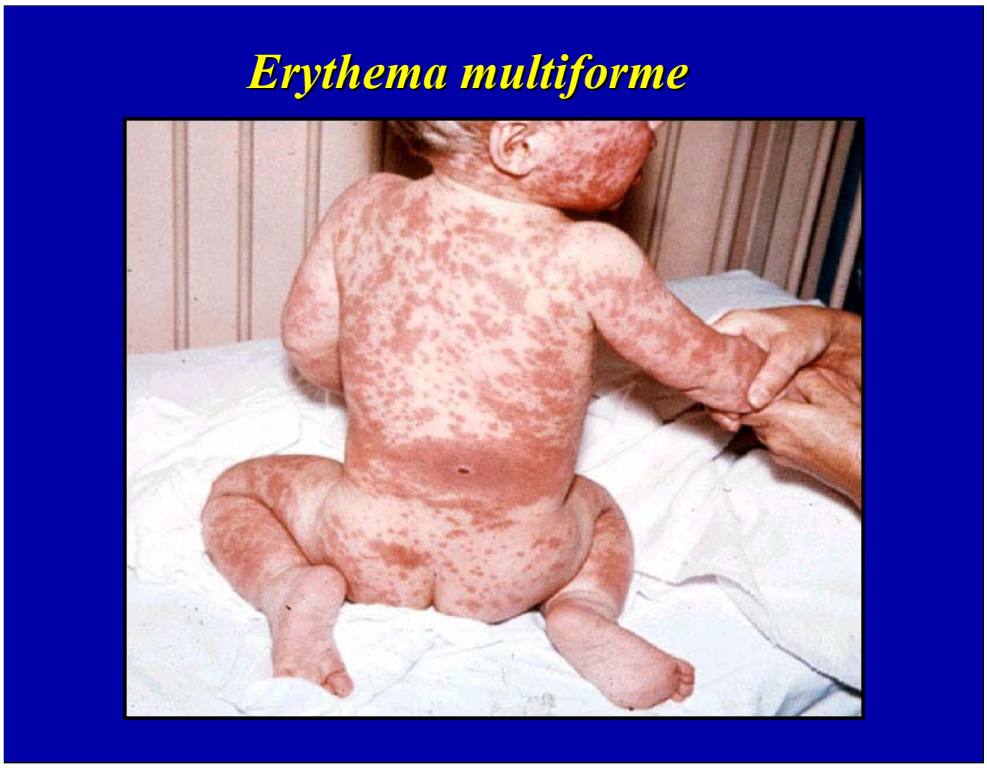
The typical lesion of erythema multiforme is described as a central, dark papule or vesicle surrounded by surrounded by a pale zone and a halo of erythema, or “bull’s eye.” This slide shows typical EM lesions, although this is not from a patient who received smallpox vaccine. EM occurs as a hypersensitivity reaction to a number of things, including drugs,and bacterial or viral infections.



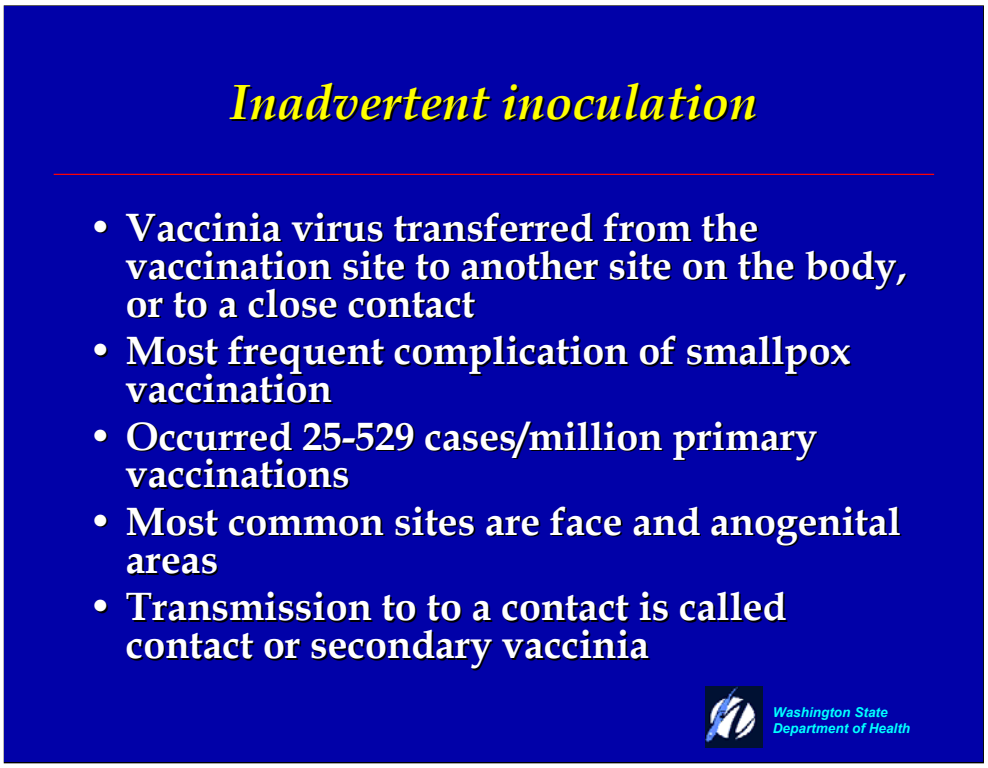
Erythema multiforme in a child – her healing vaccination site can be seen on left upper arm. The rash can be extremely itchy.



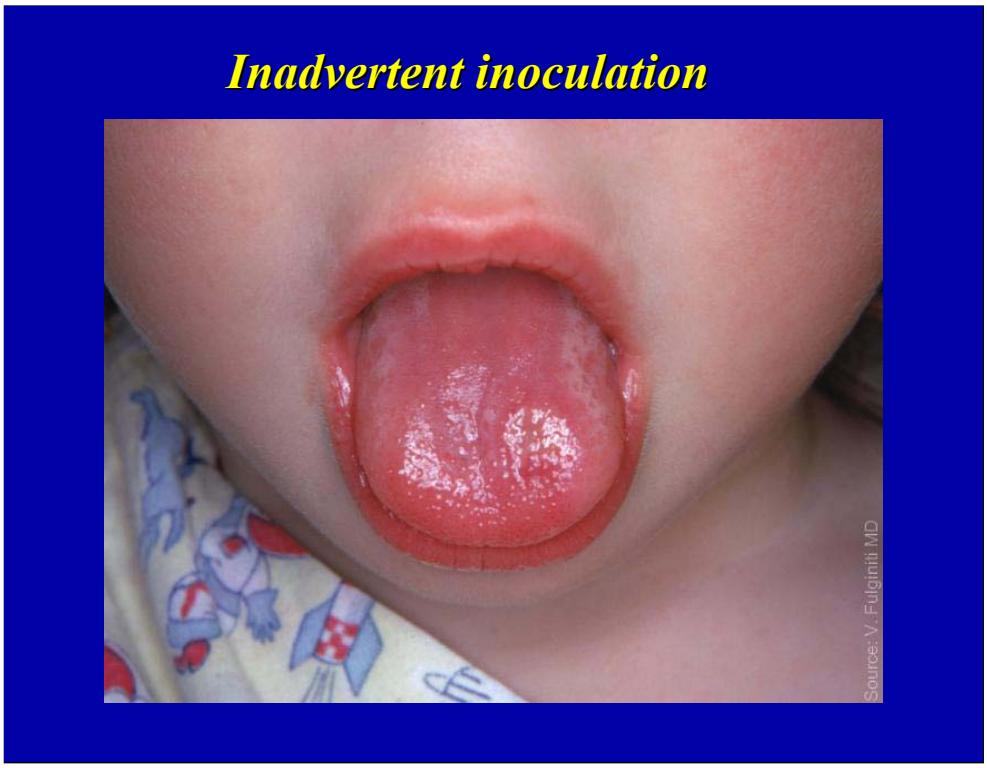
Normal, healing vaccination site with erythema multiforme; this can be distinguished from a robust primary take by the irregular edges of rash around the site and widespread distribution of the lesions.



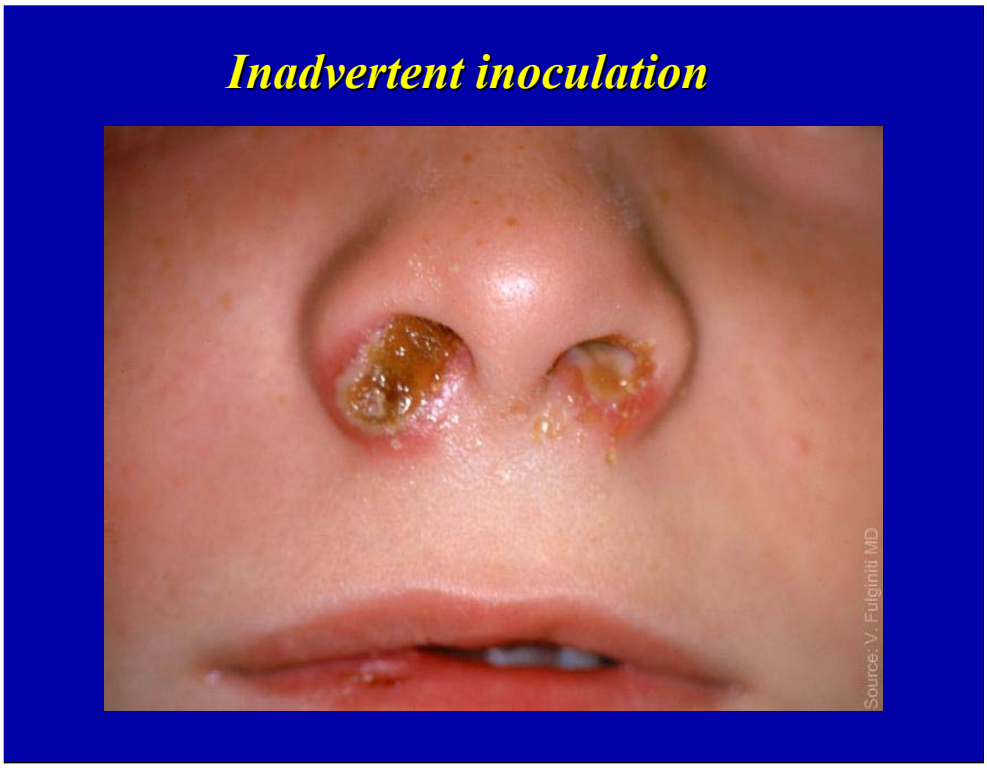
Erythema multiforme again - note the atypical location of the vaccination site, one formally used because it was thought to be less likely to be scratched or touched. Sites on the back or thigh are no longer recommended, as they tend to have higher rates of bacterial infection. In the absence of Stevens Johnson syndrome, the rash of EM usually resolves in less than a month, and can be treated with antihistamines.



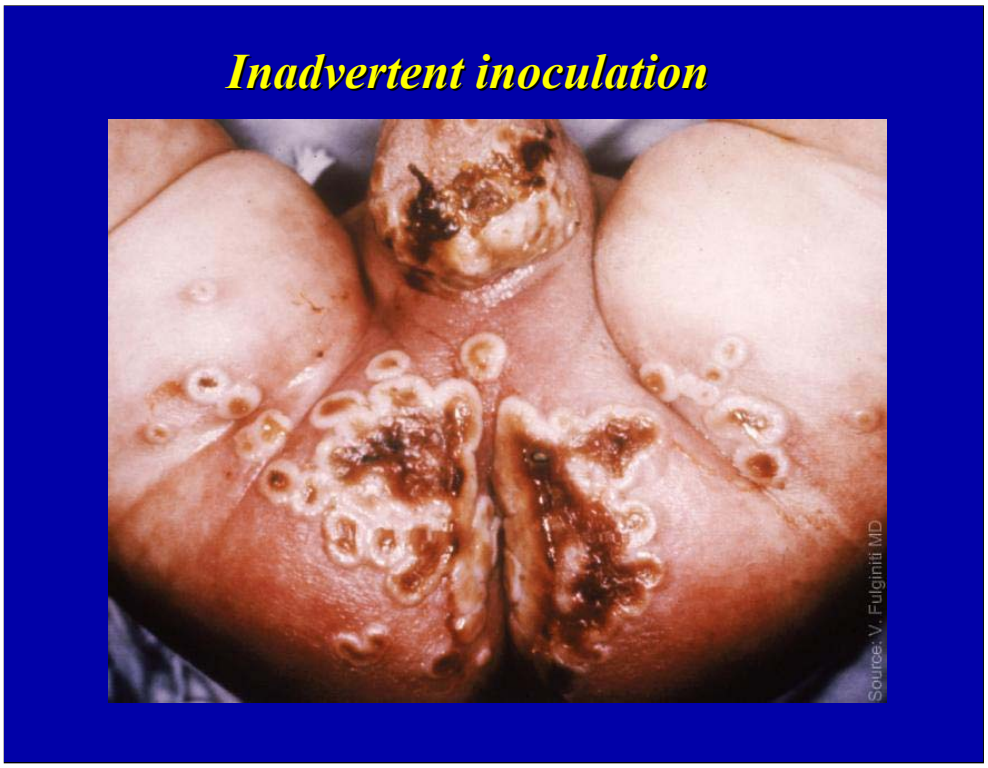
Inadvertent inoculation occurs when vaccinia virus is transferred from the vaccination site to another site on the body, or to a close contact. Inadvertent inoculation is the most common complication of smallpox vaccination, and during the years that we routinely vaccinated children, 25-529 cases occurred for each million primary vaccinations. The most common sites of inadvertent inoculation are the face and anogenital areas. Transmission of vaccine virus to a contact is called contact or secondary vaccinia.



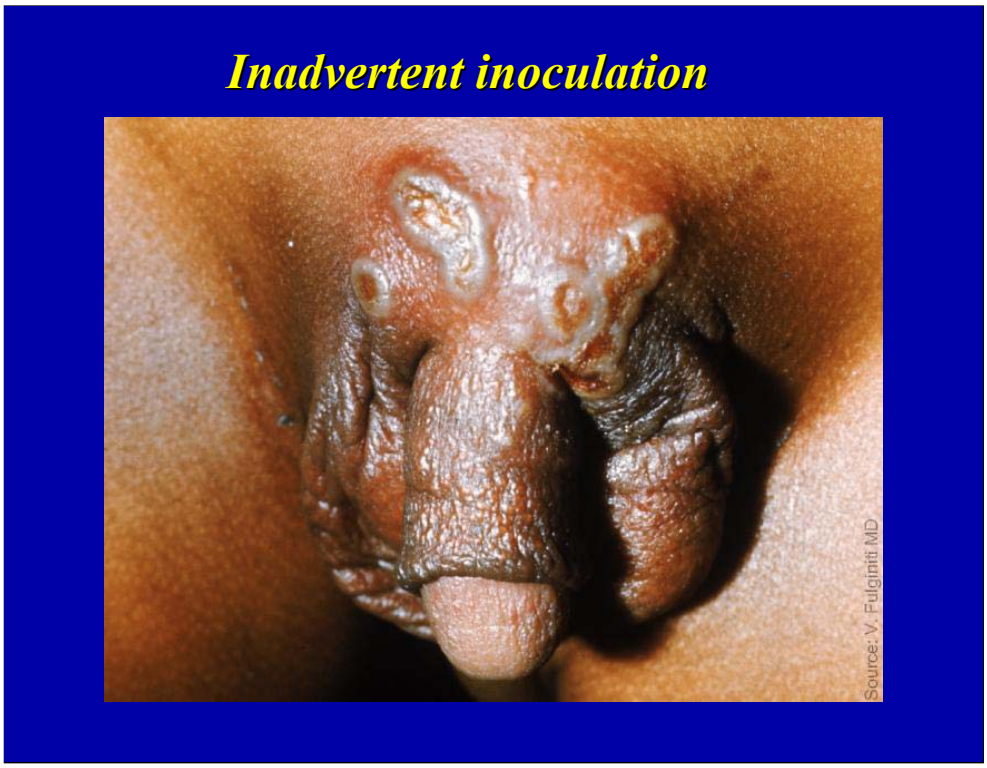
A large lesion on the anterior tongue.



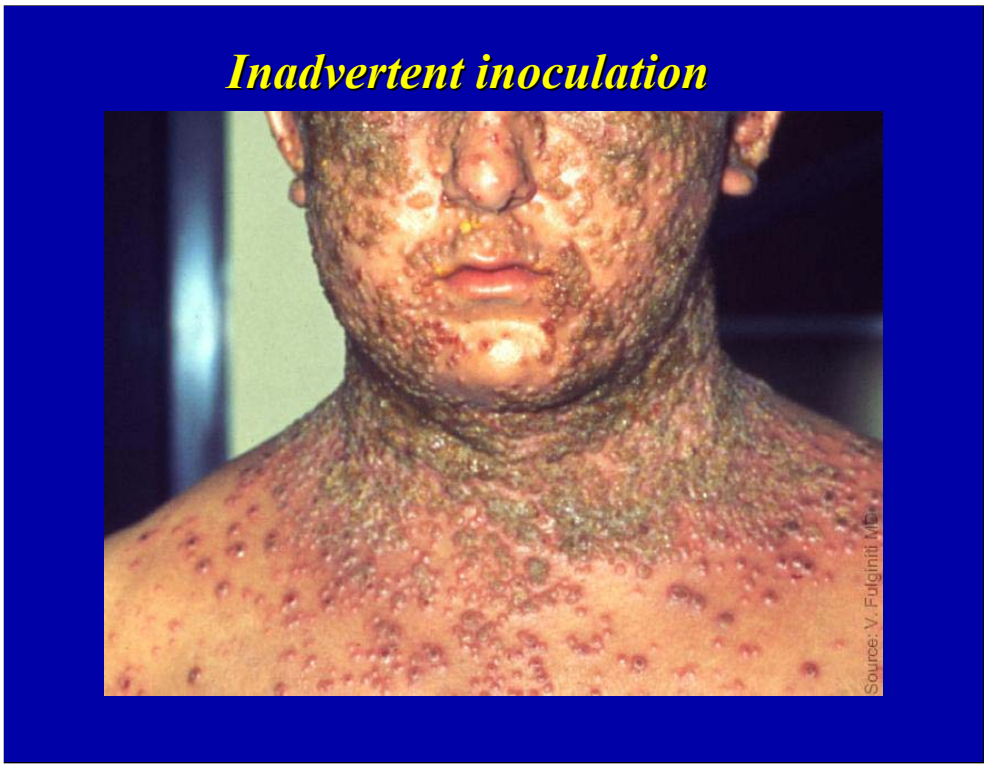
In children, the nares are a very common site for lesions.



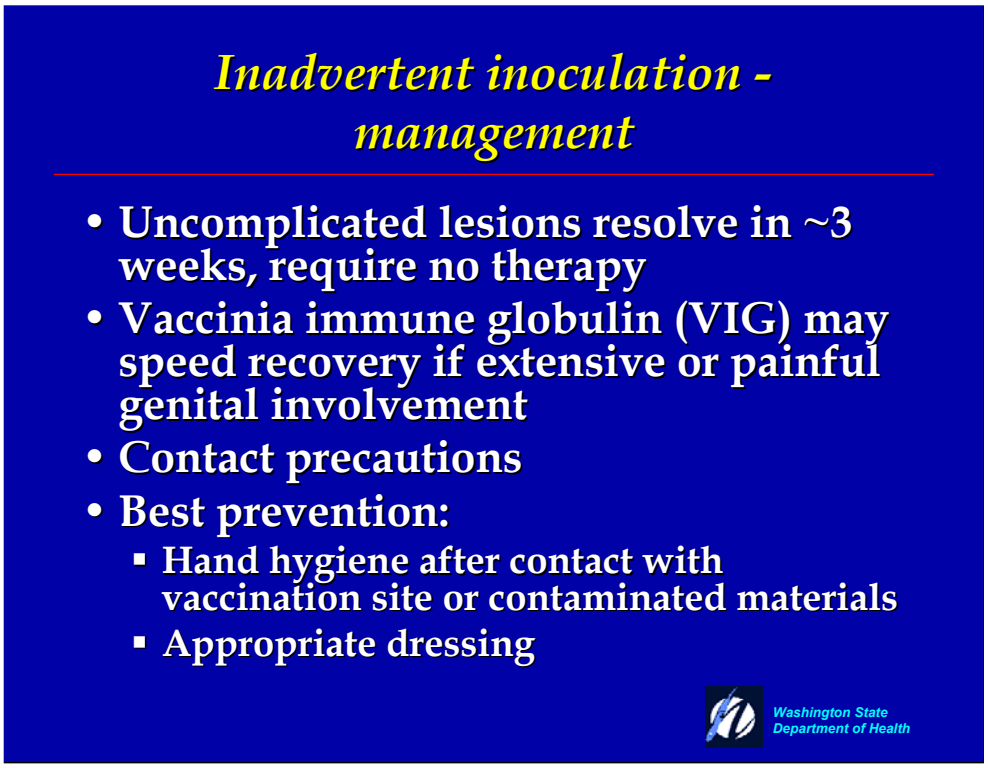
The anogenital area is also common in children, especially in kids in diapers.



The genital region can also be affected, and in an adult, may be confused with a ulcerative sexually transmitted disease.



Inadvertent inoculation is usually localized, but in individuals with breaks in the epidermis due to skin conditions, it can become more widespread. This is a man with extensive, active acne who developed widespread lesions from inadvertent inoculation, resulting in scarring.

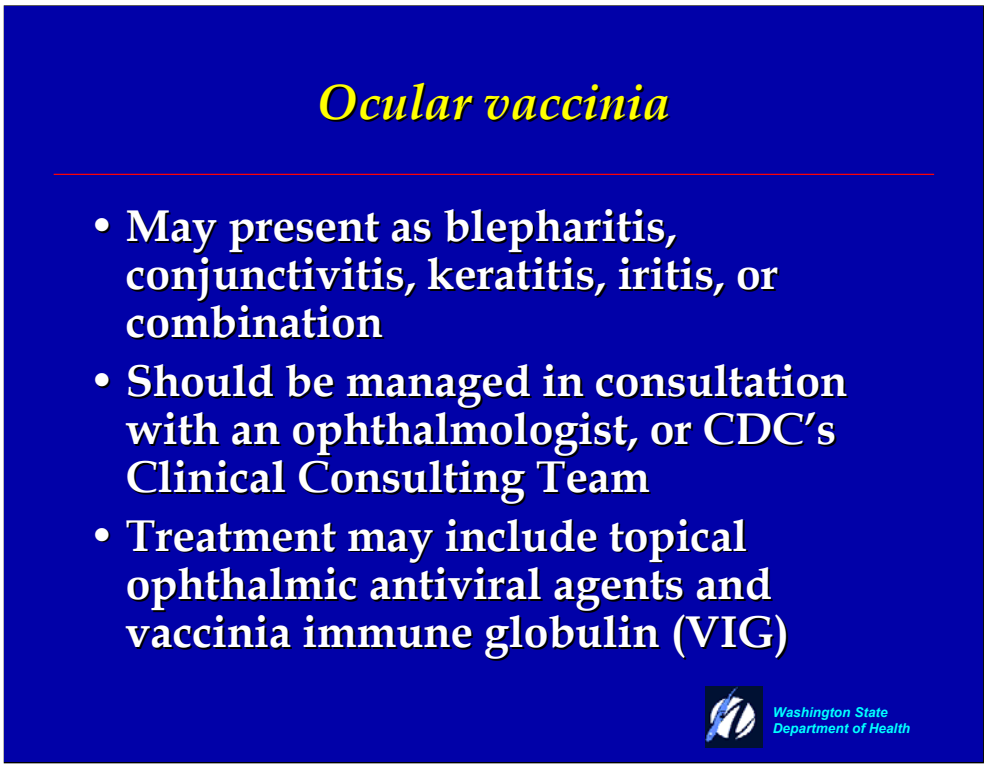


Uncomplicated lesions caused by inadvertent inoculation follow the same course as the lesion at the vaccination site, and resolve in about 3 weeks – they usually require no therapy.

Vaccinia immune globulin may speed recovery if the lesions are extensive or painful.

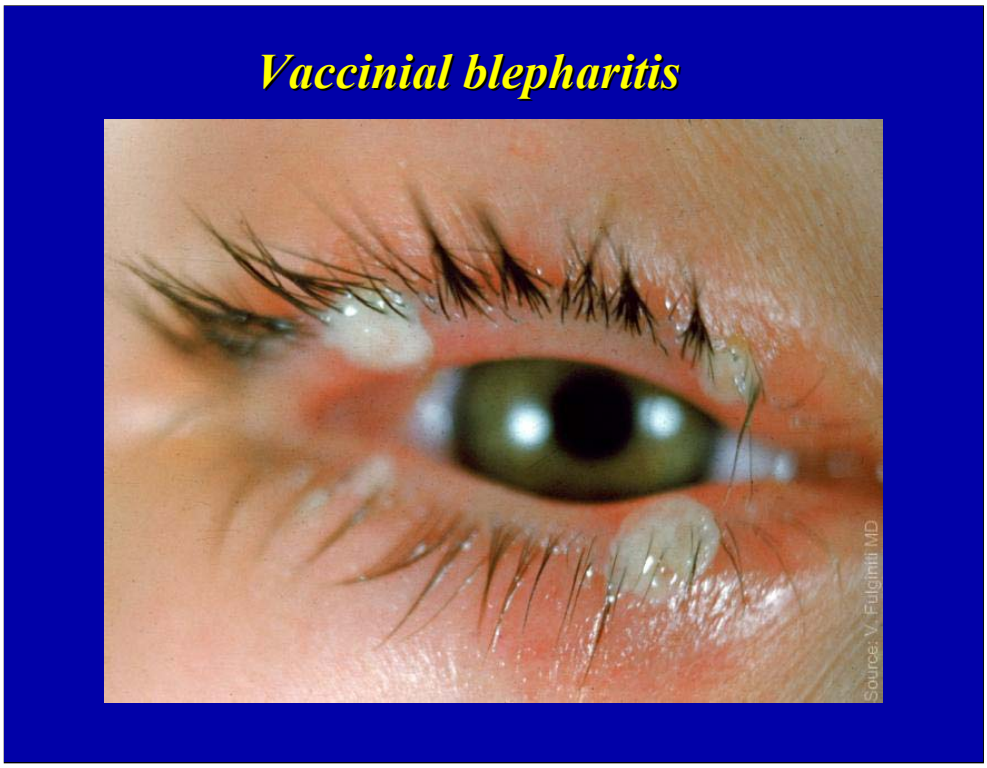
Lesions do contain vaccinia, so contact precautions are necessary.

The best prevention for inadvertent inoculation is scrupulous hand hygiene – washing with soap & water or using alcohol-based hand rubs after coming into contact with the vaccination site or contaminated materials – like vaccination dressings, or towels, clothing and sheets used by a vaccinee. In addition, personnel with direct patient contact should keep their vaccination sites dressed with gauze and a semi-permeable membrane while engaged in patient care activities, and the site should be assessed at least every other day while at work to assure proper coverage and to reinforce infections control.

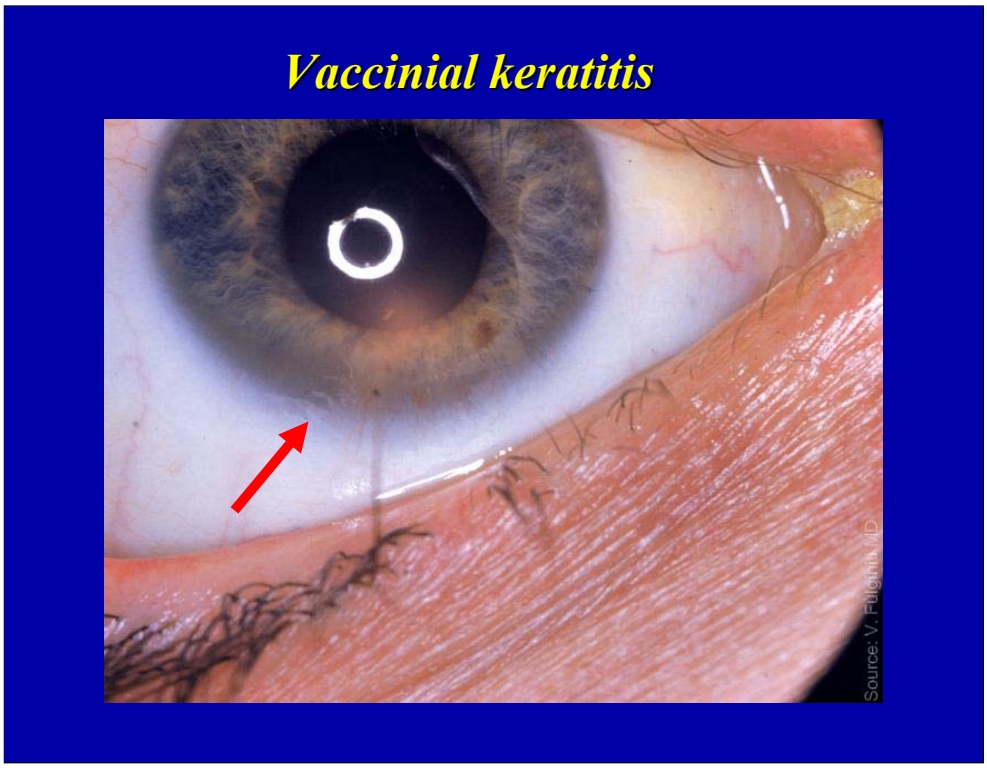


Ocular vaccinia is inadvertent inoculation with periorbital or orbital implantation of the virus. It may present as blepharitis, or inflammation of the eye lids, conjunctivitis, or with more extensive and sight-threatening complications like keratitis or iritis. All ocular vaccinia should be handled in consultation with an ophthalmologist, and or the CDC's Clinical Consulting Team. Treatment of ocular vaccinia may include topical ophthalmic antivirals and vaccinia immune globulin, however, the use of VIG in keratitis may exacerbate corneal scarring.

Lesions in the periorbital area in an adult.

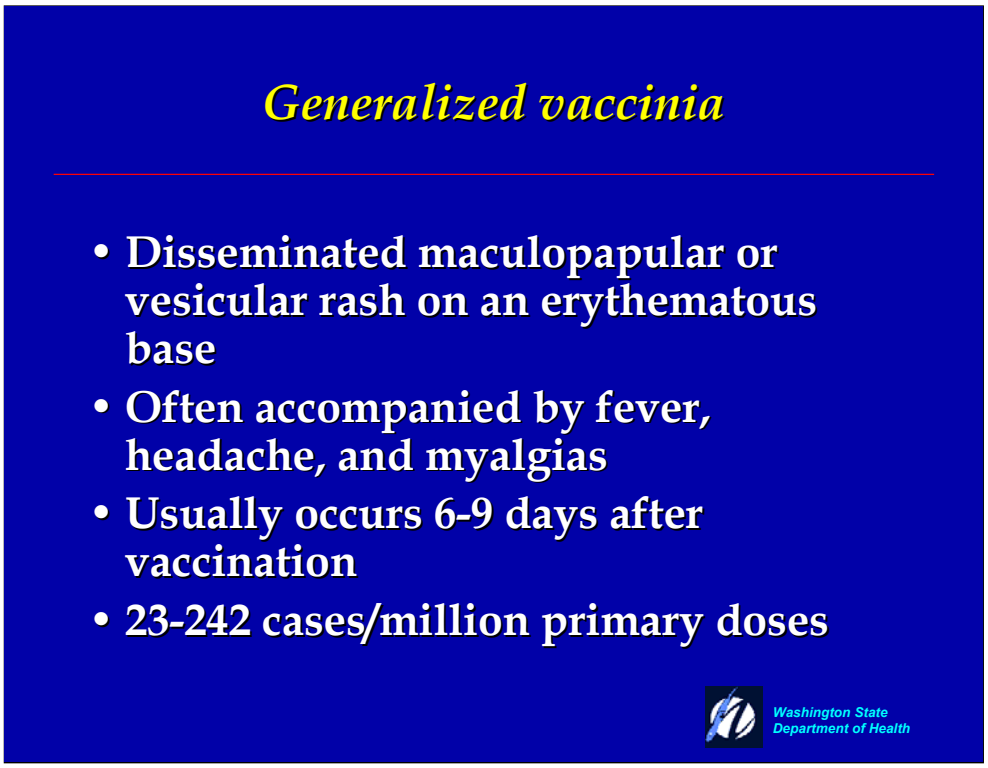


Blepharitis, following inadvertent inoculation of the eye, with lesions seen on both upper and lower lids.

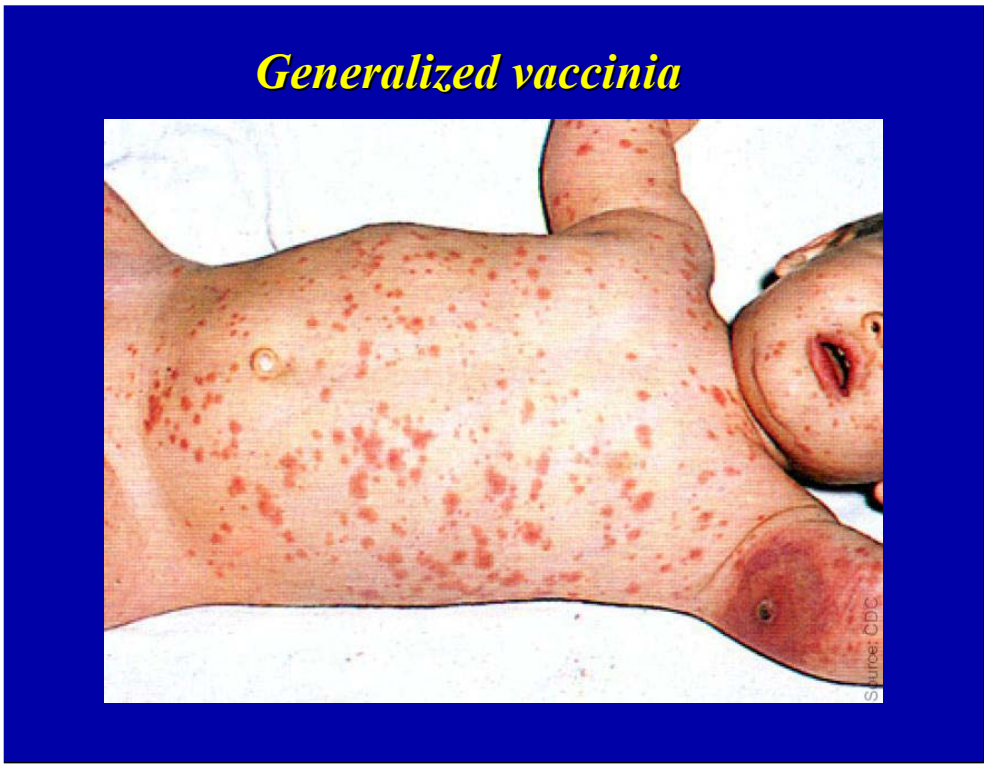


Vaccinial keratitis, in the absence of associated periorbital disease. The lesion can be seen as a subtle haziness in the inferior portion of the cornea – and would be best seen by staining and slit lamp examination.

A different patient with obvious corneal scarring. Data on ocular infections is limited, and many case series discuss treatment with older antivirals which are no longer in use. The use of VIG in ocular vaccinia is controversial, and some reports have suggested that sequelae are more common in patients with keratitis treated with VIG. Because so little is known about the treatment of this complication, it's recommended that ocular vaccinia be handled in consultation with an ophthalmologist, or the CDC's Clinical Consulting Team. Later, I will discuss how to obtain a consultation.



Generalized vaccinia is characterized by a disseminated maculopapular or vesicular rash, usually on an erythematous base. Patients with GV often have fever, headache and myalgias, but in general, they do not appear acutely ill. GV usually appears from 6-9 days after vaccination, and in the past the incidence ranged from 23-242 cases/million primary vaccine doses.

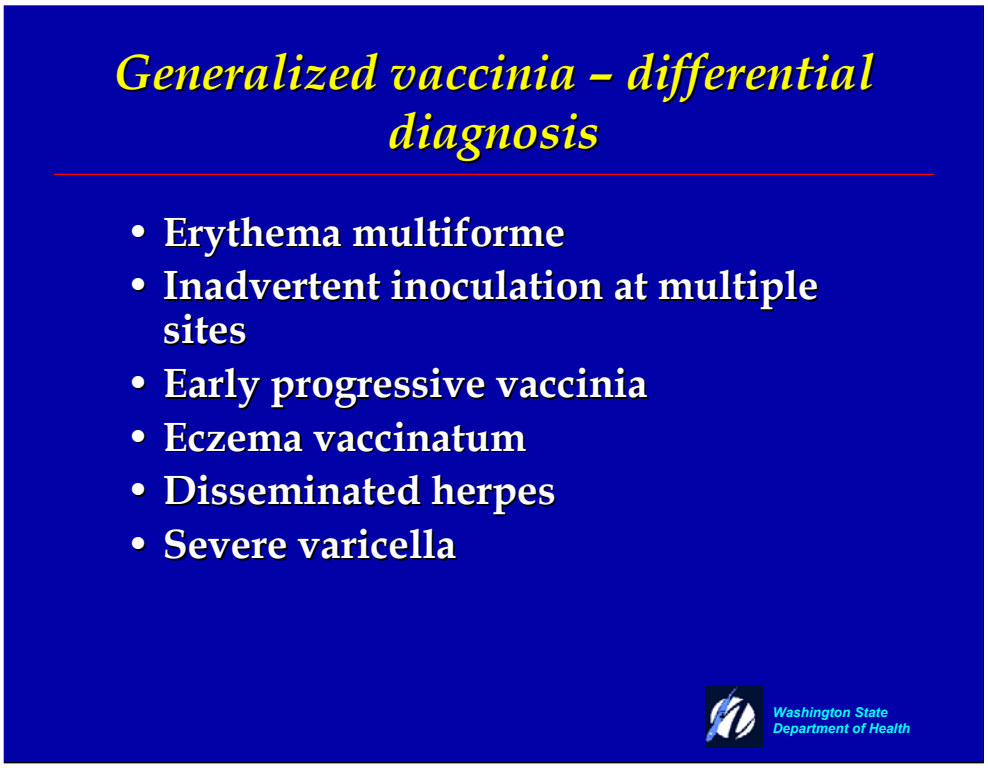


Generalized vaccinia in a child, with the vaccination site under the left arm.

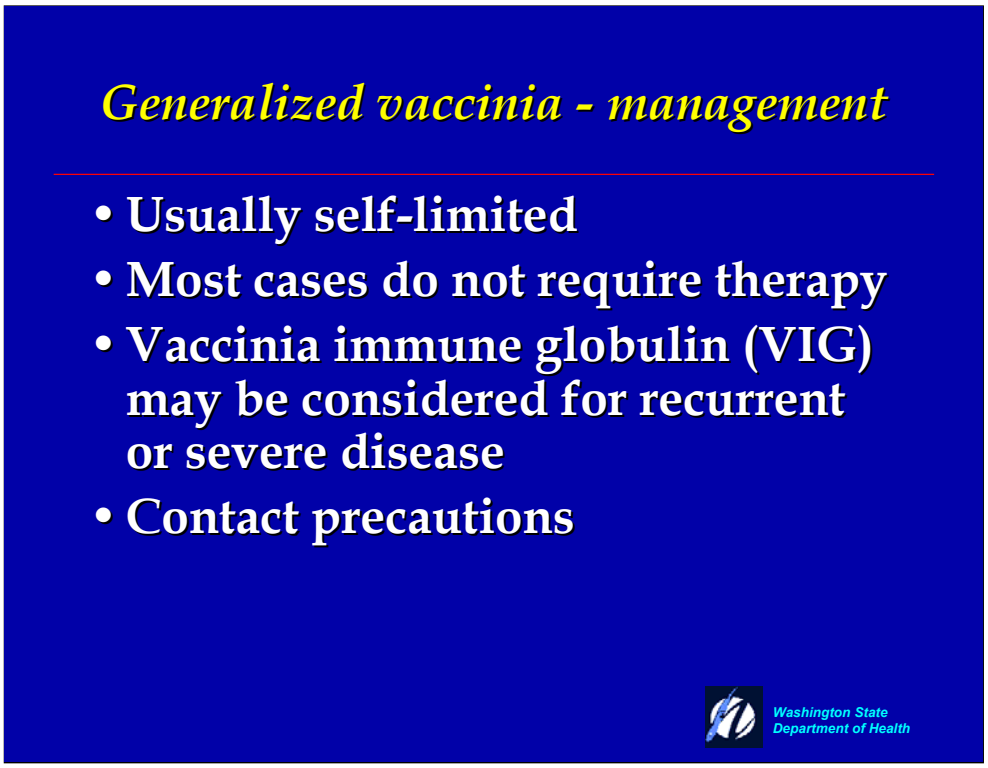
A different child with generalized vaccinia, Not happy, but not particularly toxic either.

Generalized vaccinia – localized lesions

Rarely in generalized vaccinia, the rash may be localized; it can also appear on the palms & soles. Sometimes the appearance of the rash is very similar to smallpox.

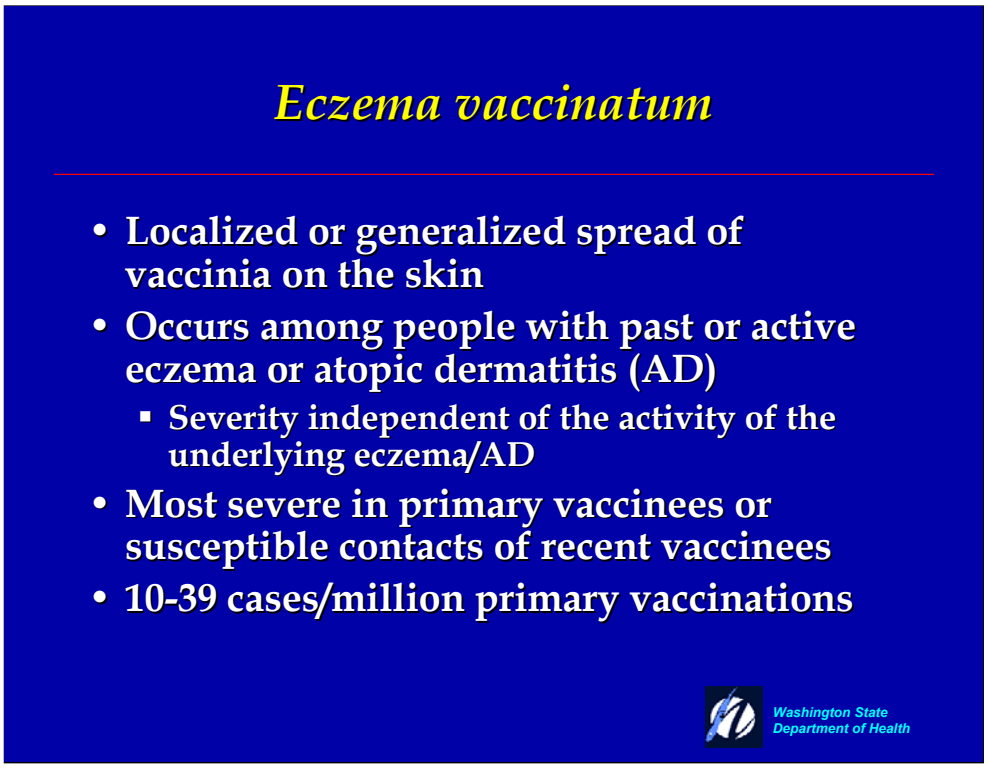


The differential of generalized vaccinia includes several other adverse events associated with vaccinia vaccine, as well as other viral infections. It can usually be distinguished from erythema multiforme, inadvertent inoculation, and progressive vaccinia by the appearance of the lesions. In eczema vaccinatum, patients appear quite ill, and may have a history of prior skin disease. Patients with disseminated herpes or varicella infection also appear ill, may lack a history of recent vaccination or exposure to vaccinia, and may have positive results of rapid diagnostic testing for herpes simplex or varicella zoster viruses.

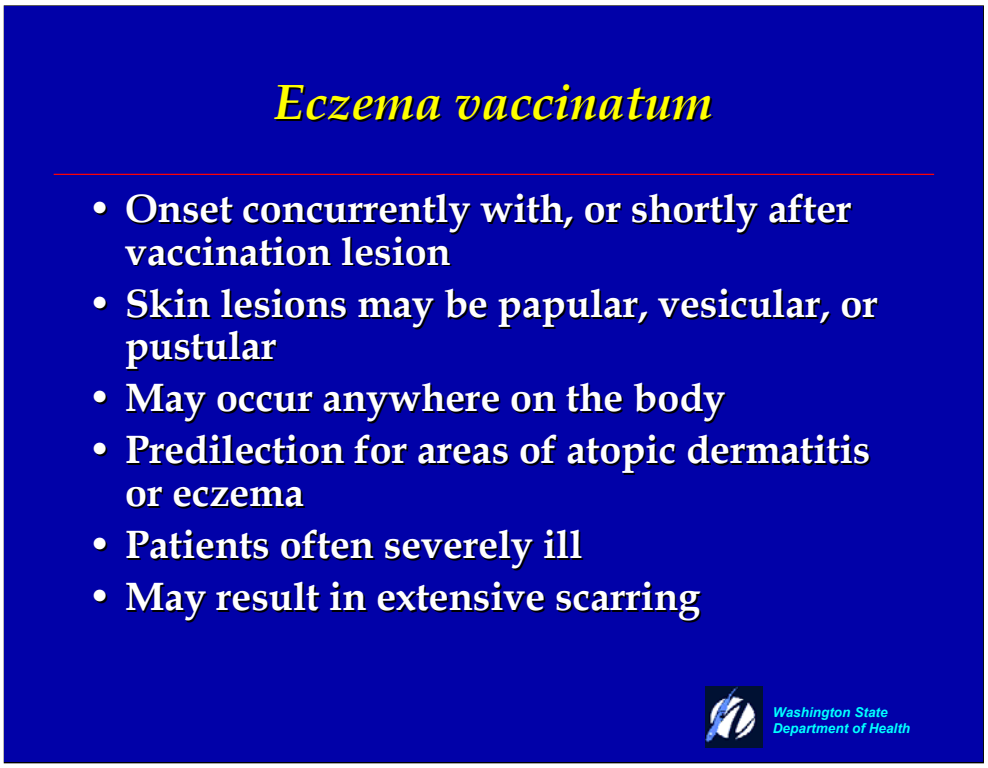


Generalized vaccinia is usually self-limited in healthy patients, and most will not require specific therapy. For the rare patient who has recurrent or severe disease, vaccinia immune globulin may be indicated.

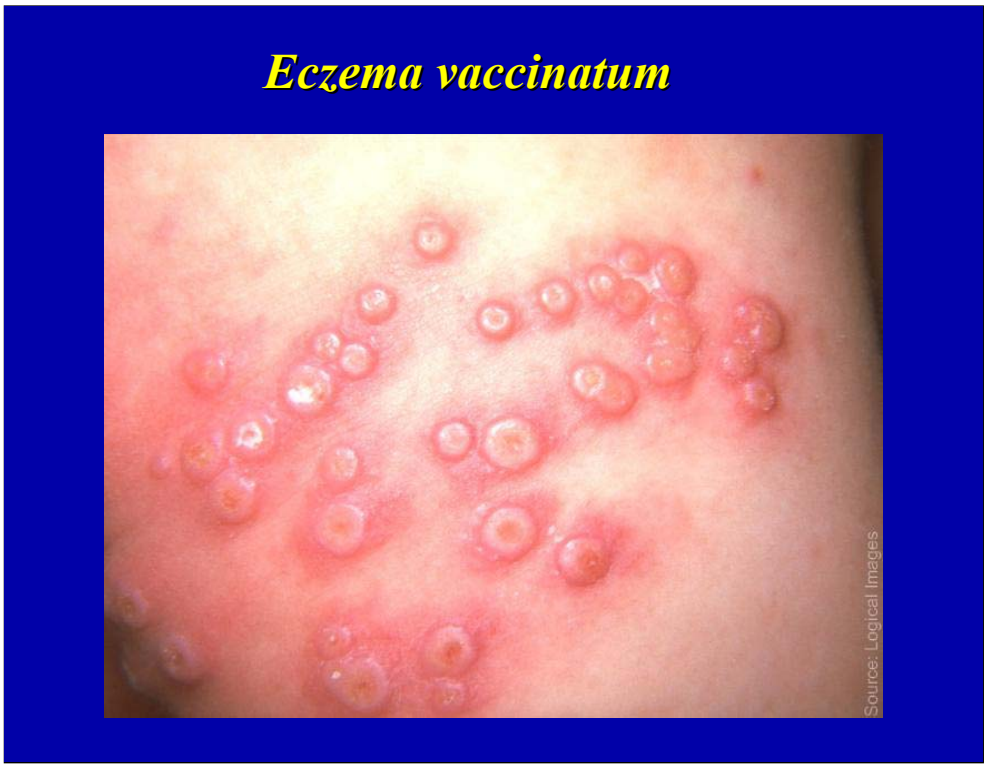
The distribution of the rash suggests that it results from hematogenous spread of the virus, although it is unknown if vaccinia is present in the lesions. Because of uncertainty, these patients should be handled with contact precautions.



Eczema vaccinatum (EV) is a localized or generalized spread of vaccinia on the skin. EV occurs almost exclusively among people who have past or active eczema or atopic dermatitis (AD). The severity of EV is independent of the activity of the underlying skin disease. EV is most severe in primary vaccinees or susceptible contacts of recent vaccinees. During routine vaccination programs in the 1960 & 70s – there were 10-39 cases of EV/million primary vaccinations.



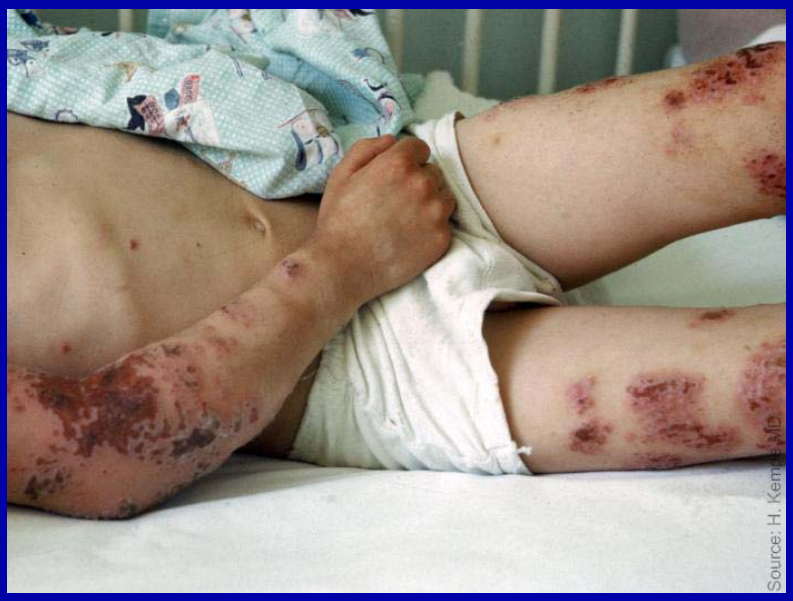
The onset occurs concurrently with, or shortly after vaccination lesion appears. Skin lesions may be papular, vesicular, or pustular and may occur anywhere on the body, but have a predilection for areas affected by atopic dermatitis or eczema. Patients may have fever, lymphadenopathy, malaise, and are often severely ill. Eczema vaccinatum may be life-threatening and result in extensive scarring.



Typical early, localized lesions of eczema vaccinatum. Each umbilicated vesicle resembles a normal vaccination site.

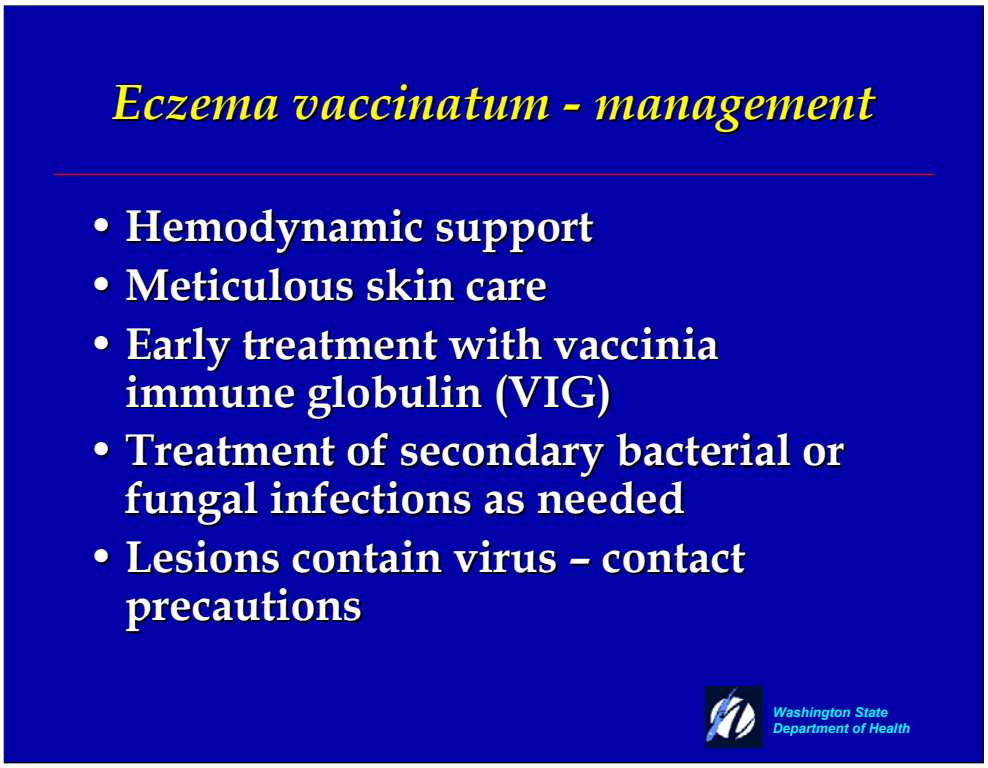
In young children and adults, lesions are frequently seen on the face and neck, sites most commonly affected by atopic dermatitis in these age groups. You can see from this child that skin involvement can be extensive. Secondary bacterial and fungal infections may complicate the course of some patients, and many will require admission to a burn unit for specialized care.

Eczema vaccinatum



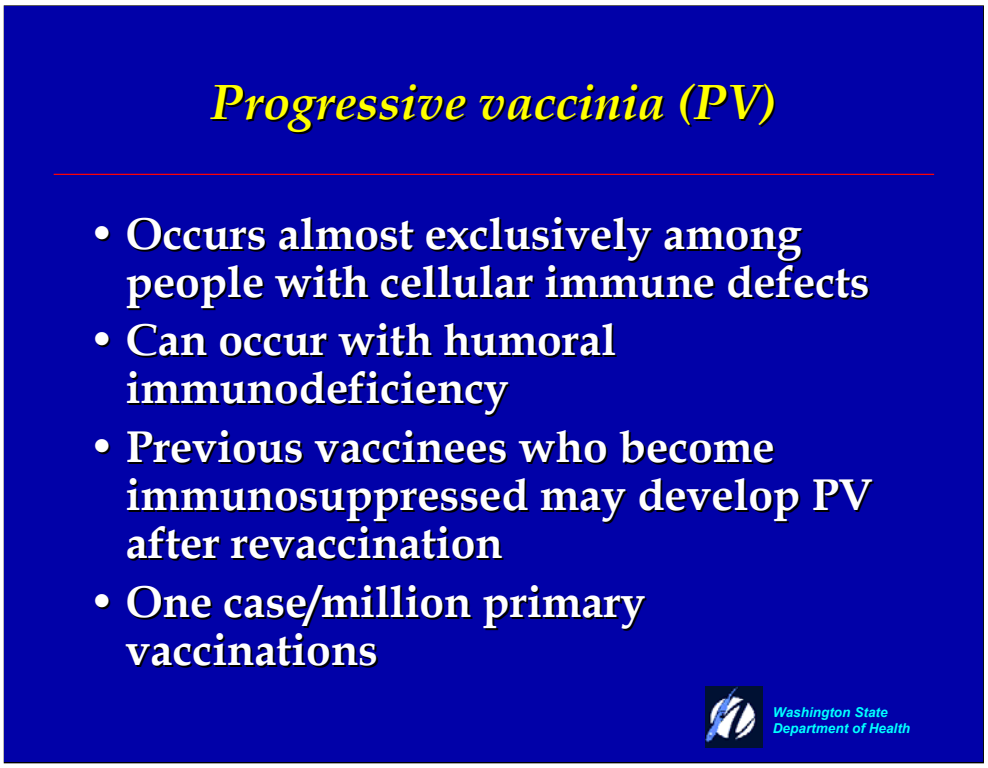
In older children, lesions are seen on the flexor surfaces of the arms & legs, but may spread from there. This young boy has lesions in the flexoral surfaces of his arms & legs, but the lesions have also extended to involve the extensor surfaces.

This is an adult who was the intimate contact of a military vaccinee in the 1980s; she developed extensive eczema vaccinatum, with subsequent scarring.



Most patients with eczema vaccinatum will be seriously ill and will require hospitalization for hemodynamic support and meticulous skin care. Early treatment with vaccinia immune globulin is essential, especially in extensive disease in very young children. Treatment of secondary bacterial or fungal infection may be necessary.

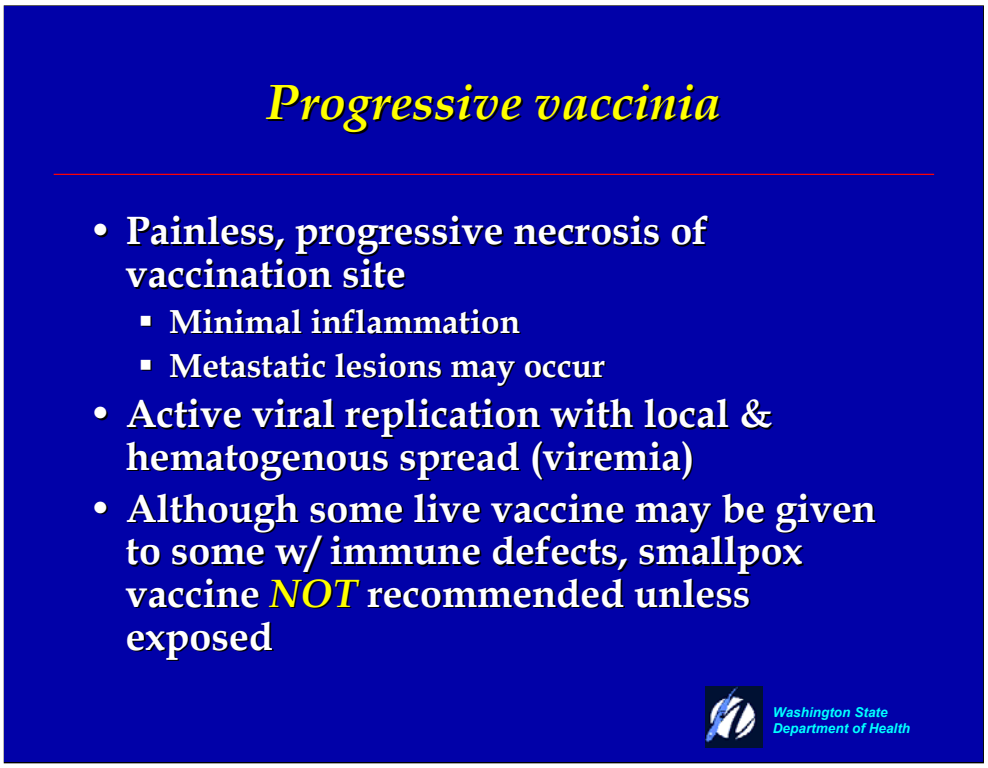
The skin lesions contain high titers of vaccinia, and patients require contact precautions.



Progressive vaccinia is an adverse event that occurs almost exclusively among people with cellular immune defects – for example, HIV infection, those on immunosuppressive drugs for treatment of malignancies, or following an organ or stem cell transplant. It can also occur with humoral immunodeficiency – for example, hypogammaglobulinmenia.

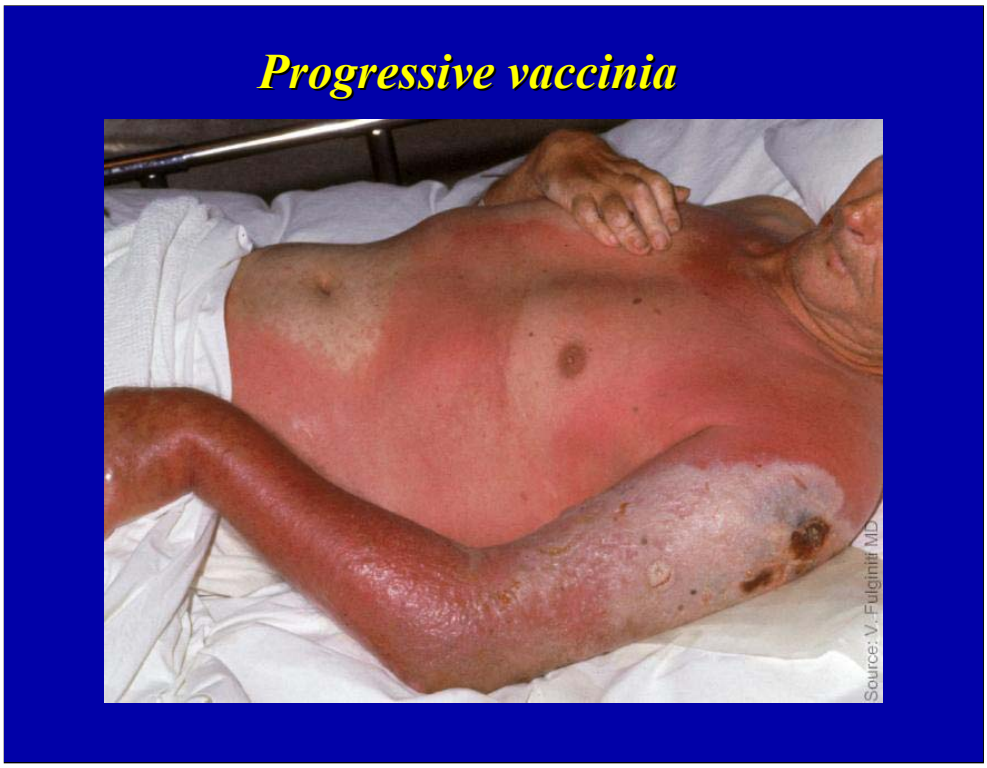
Previous vaccinees who have since become immunosuppressed may develop progressive vaccinia after revaccination.

In the past, about one case occurred per million primary vaccinations.



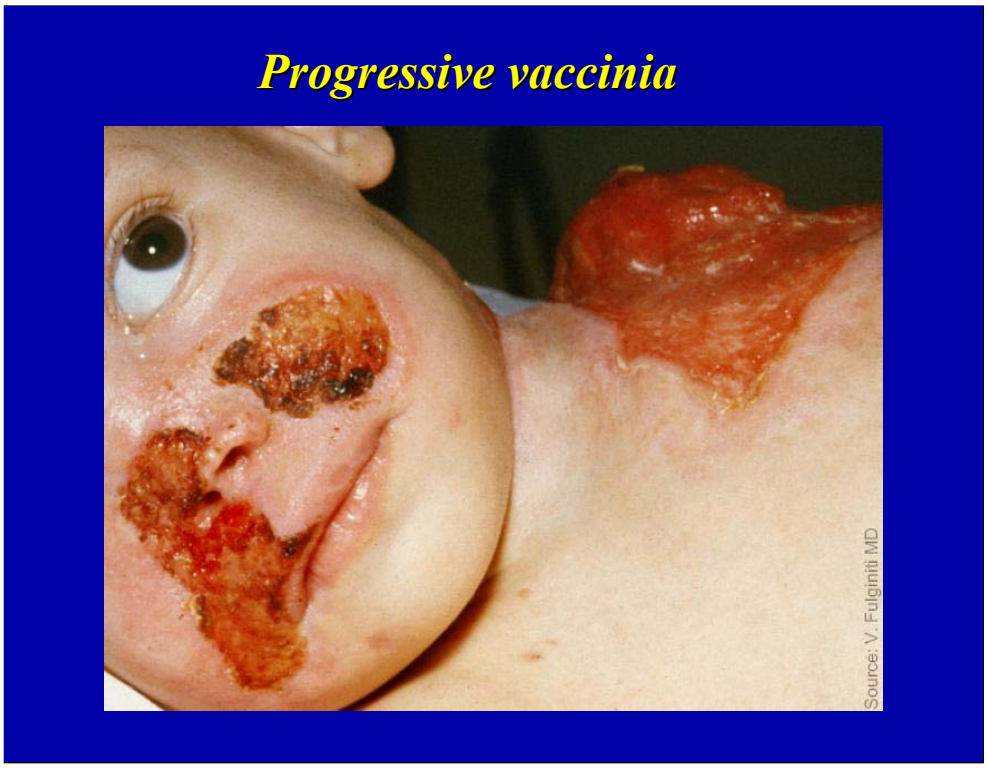
Progressive vaccinia is characterized by painless, progressive necrosis of the vaccination site. There is minimal inflammation at the site, and metastatic lesions may occur in adjacent or distant sites.

The lesions represent active viral replication uncontrolled by a defective immune system, with local and hematogenous spread. Although some live vaccines may be given to some individuals with immune defects, smallpox vaccine is not recommended for anyone with a known immunodeficiency unless they have been exposed to smallpox.

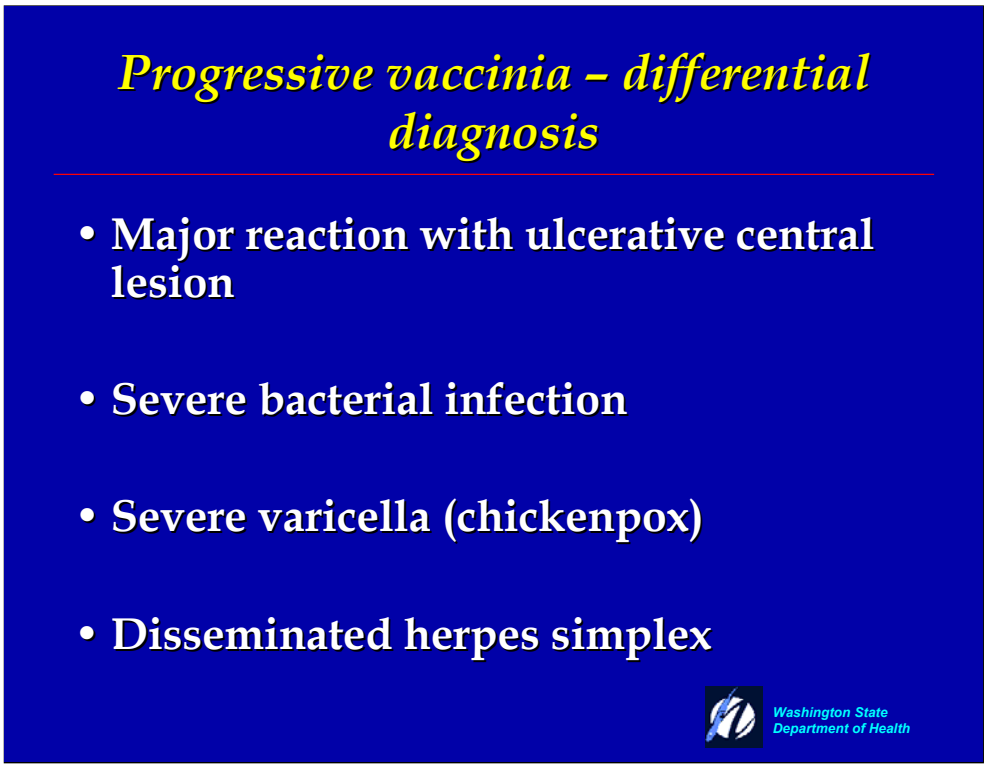


Here is an adult with lymphosarcoma who received vaccinia vaccine as treatment for a herpes infection, a form of therapy tried w/o success in the 1970s. He had progressive necrosis that began at the site of his vaccination on his left upper arm.

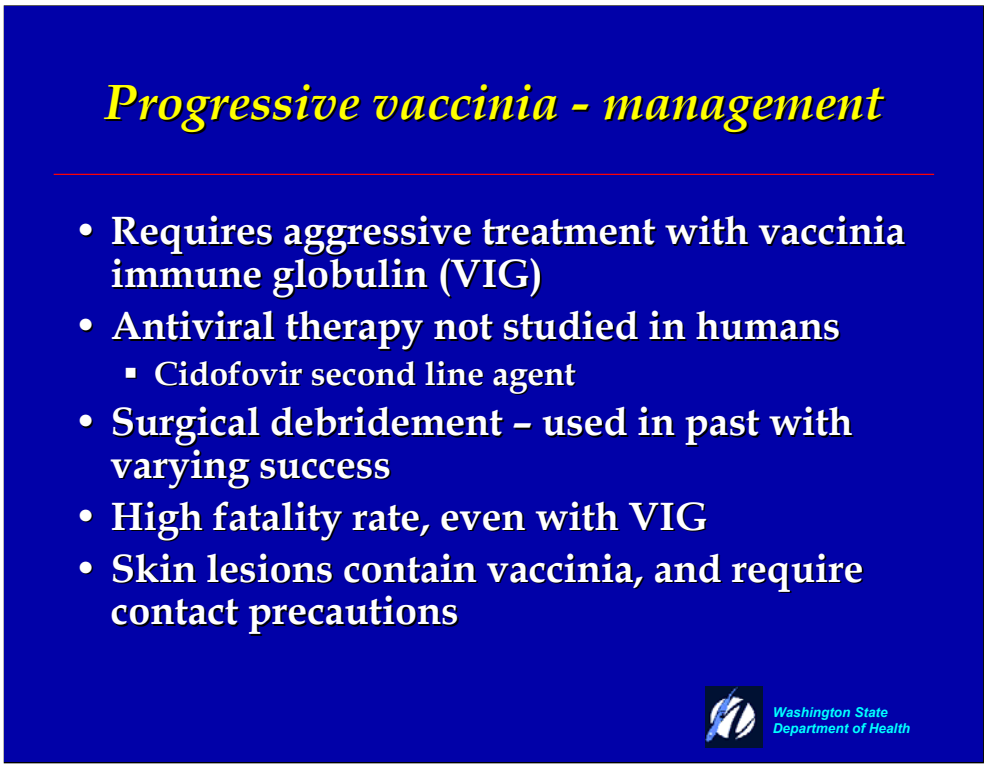
A child with hypogammaglobulinemia with metastatic or possibly inadvertent inoculated lesions of vaccinia on the face.



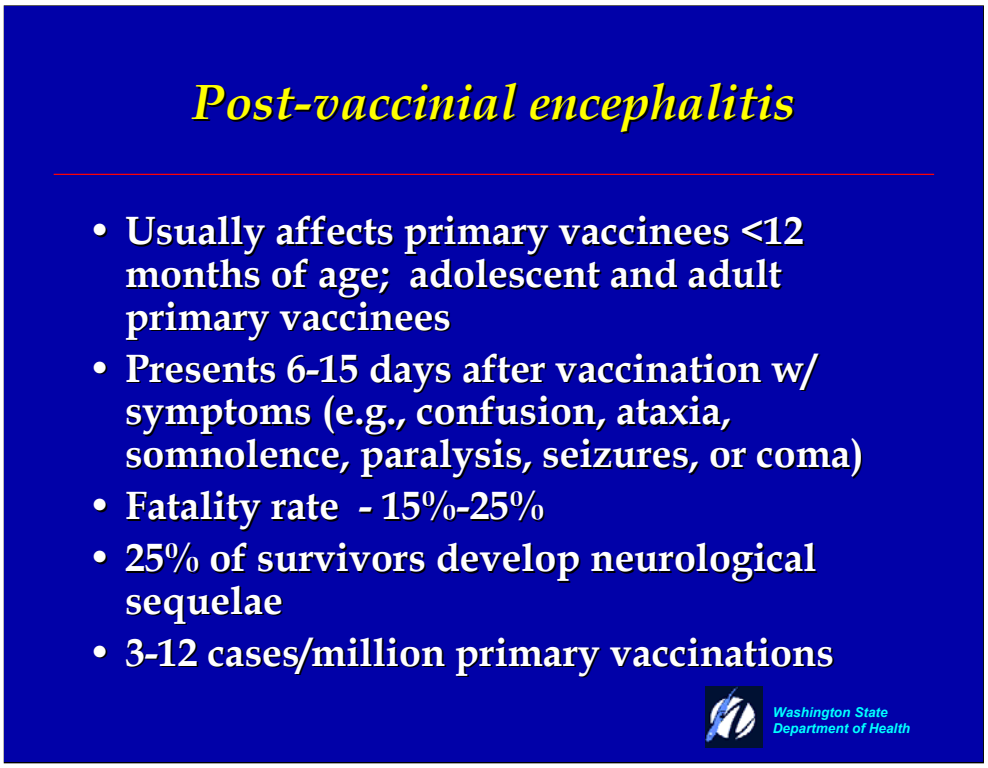
Same child a little later with a view that shows continued necrosis at the site where his left arm was amputated for progressive vaccinia extending from his original vaccination site.



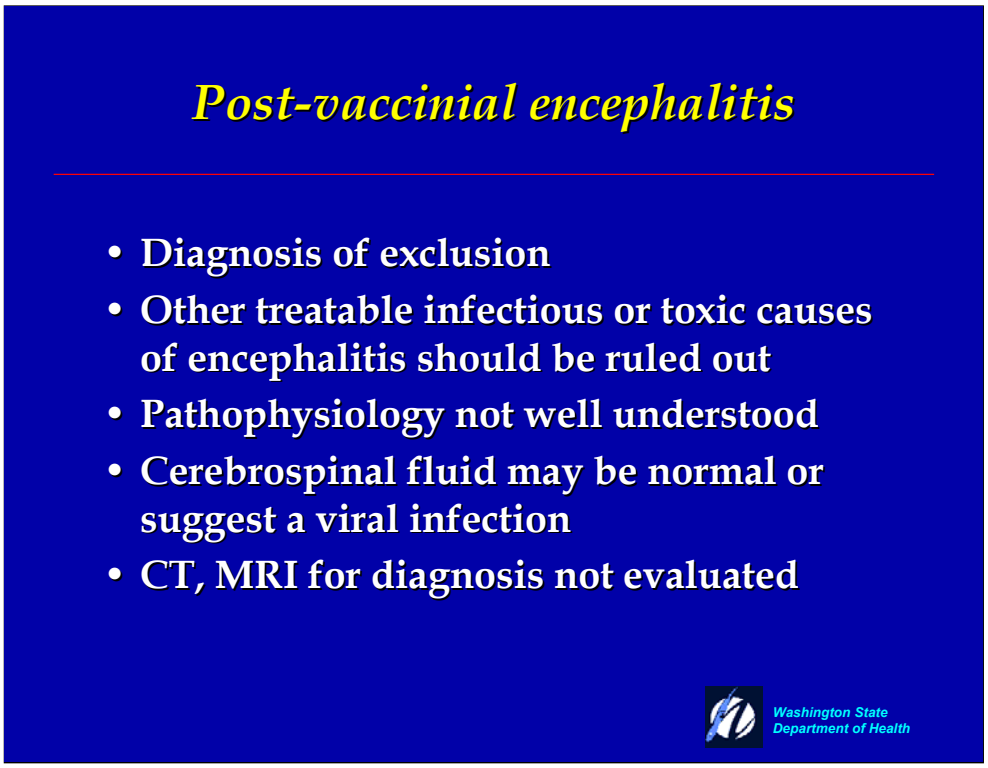
The differential diagnosis of progressive vaccinia includes a number of conditions – a normal major reaction may have an ulcerative central lesion after the vesicle erodes, but these usually reach a peak and begin to heal two weeks after vaccination, and are accompanied by the inflammation typical of a normal immune response. Severe bacterial infection may be difficult to distinguish from PV, but patients with bacterial infections usually have an intense inflammatory reaction with systemic symptoms, and may lack a history of an immune deficiency. Varicella is unlikely to be localized, and can be diagnosed with rapid testing, as can herpes simplex virus infections; in addition, there may be no history of a recent smallpox vaccination



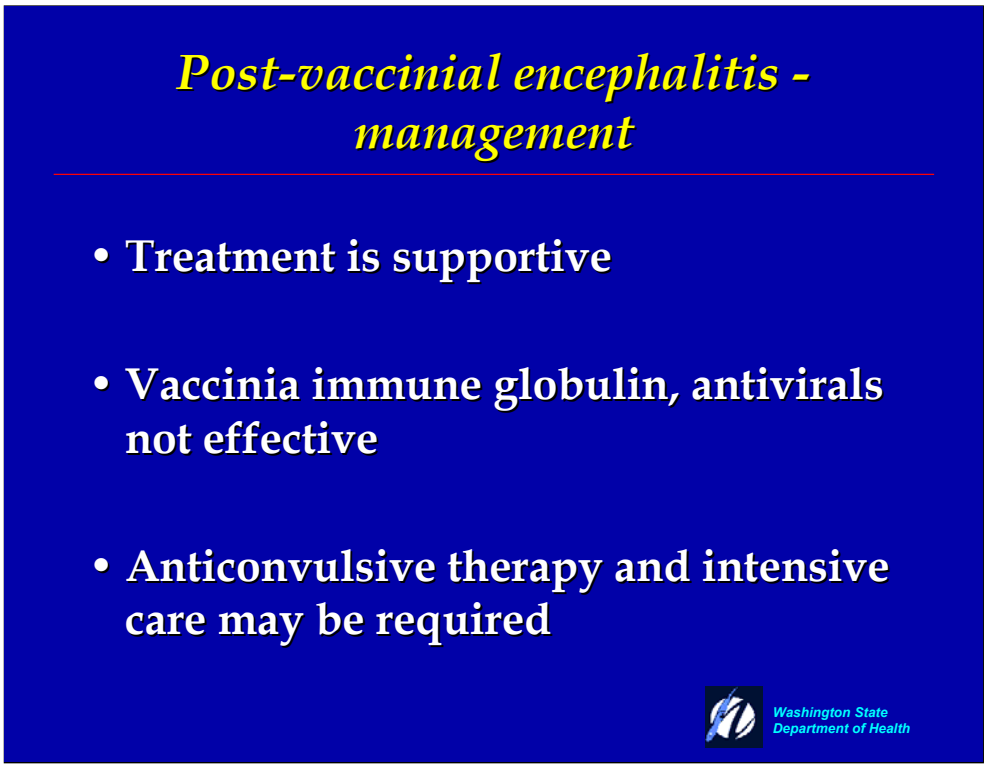
Progressive vaccinia requires aggressive treatment with vaccinia immune globulin (VIG). Antivirals therapy for PV has not been studied in humans – therefore, cidofovir is a second line agent, and would be reserved for a case in which VIG was contraindicated or clearly not effective. Surgical debridement was used in the past, particularly before VIG was available, with varying degrees of success. The fatality rate of PV is high, despite treatment with VIG. The skin lesions contain vaccinia, and contact precautions are recommended



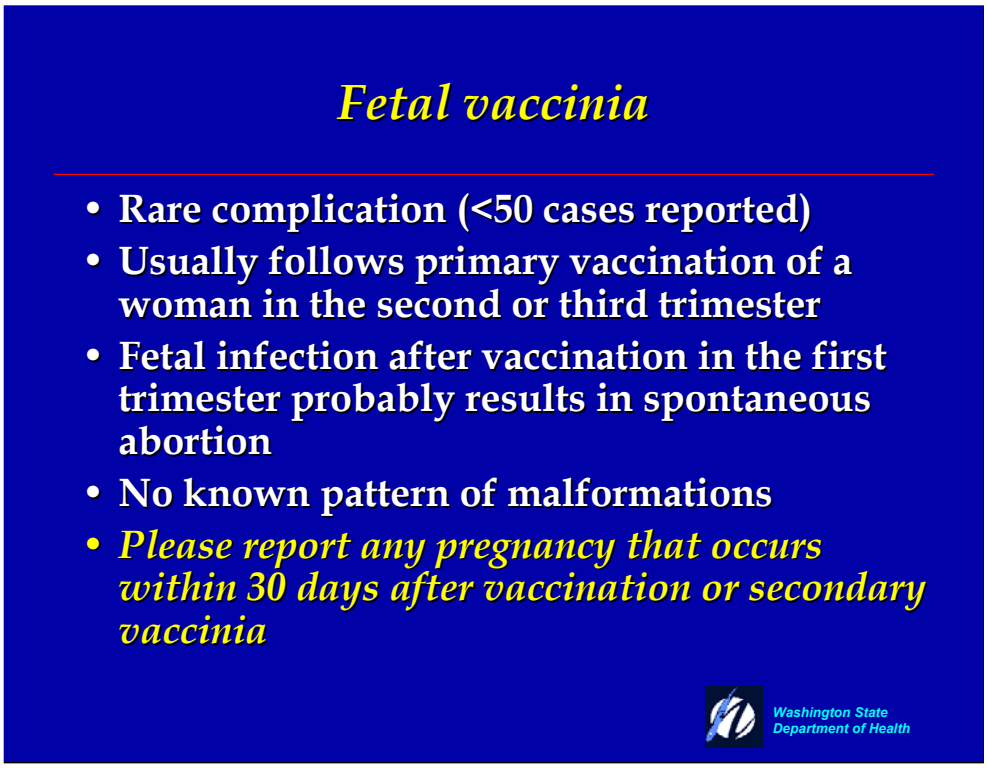
Post-vaccinial encephalitis, or encephalomyelitis, usually affects primary vaccinees <12 months of age adolescents & adults. PVE presents between 6-15 days after vaccination with symptoms similar to other causes of encephalitis: confusion, ataxia, somnolence, paralysis, seizures or coma. The fatality rate is 15-25% and 25% of survivors have significant neurological sequelae. In the past, there were 3-12 cases per million primary vaccinations



Post-vaccinial encephalitis a diagnosis of exclusion; no clinical criteria, radiographic or laboratory findings are specific for PVE, and other treatable infectious or toxic causes of encephalitis should be ruled out. The pathophysiology of PVE is not well understood, but is believed to be immune-mediated. The cerebrospinal fluid findings may be normal or suggest a viral process, but nonspecific. The use of CT or MRI scanning for diagnosis of PVE has not been evaluated, as most cases occurred before CT and MRI technology were widely available.



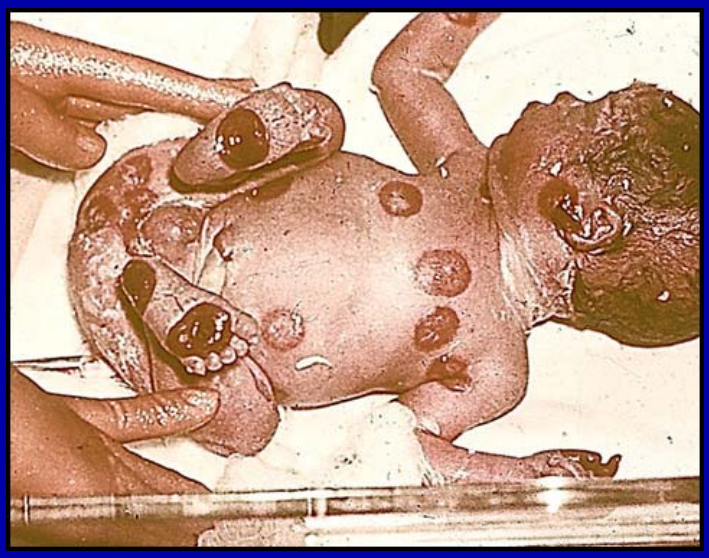
The treatment of post-vaccinial encephalitis is supportive, and vaccinia immune globulin or antivirals are not effective. Anticonvulsant therapy and intensive care may be required. Because there is no active vaccinia virus present, standard precautions are sufficient.



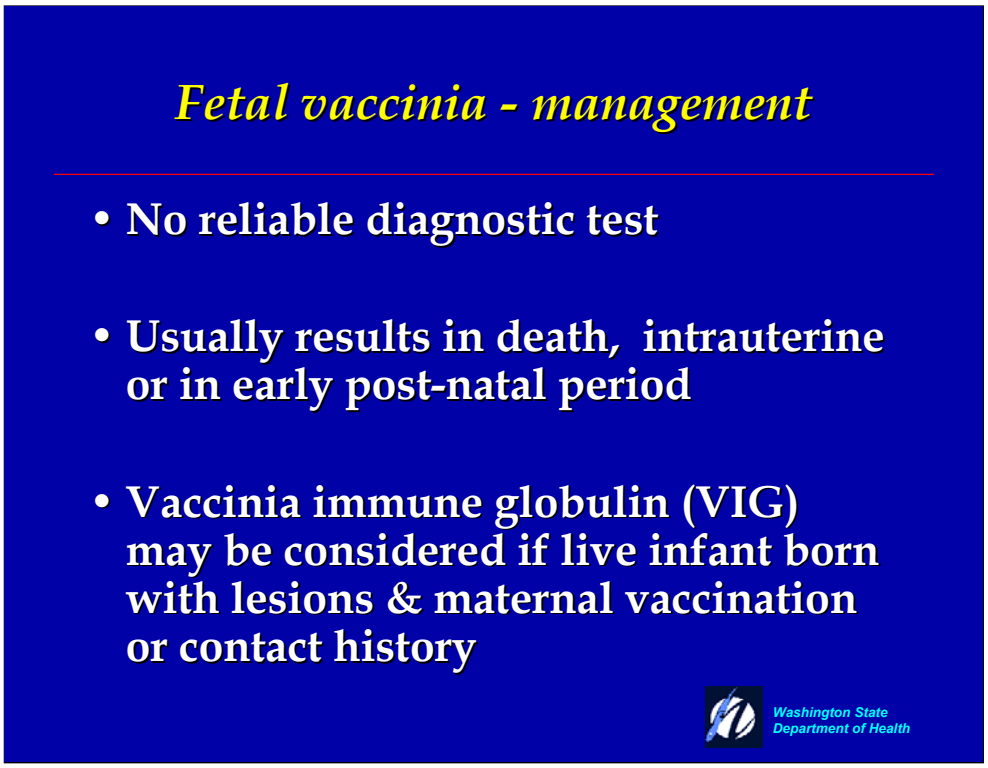
Fetal vaccinia is a rare complication of smallpox vaccination – less than 50 cases reported in the literature. It usually follows primary vaccination of a woman during the second or third trimester of pregnancy, but has also been reported in pregnant contacts of vaccinees. Fetal infection after vaccination in the first trimester probably results in spontaneous abortion. There are no known patterns of congenital malformations associated with vaccination during pregnancy.

Because so little is known about the effects of smallpox vaccine on pregnancy, it is important to report any pregnancy that occurs within 30 days after receipt of smallpox vaccine or secondary vaccinia, so the data can become part of the National Vaccinia in Pregnancy Registry.

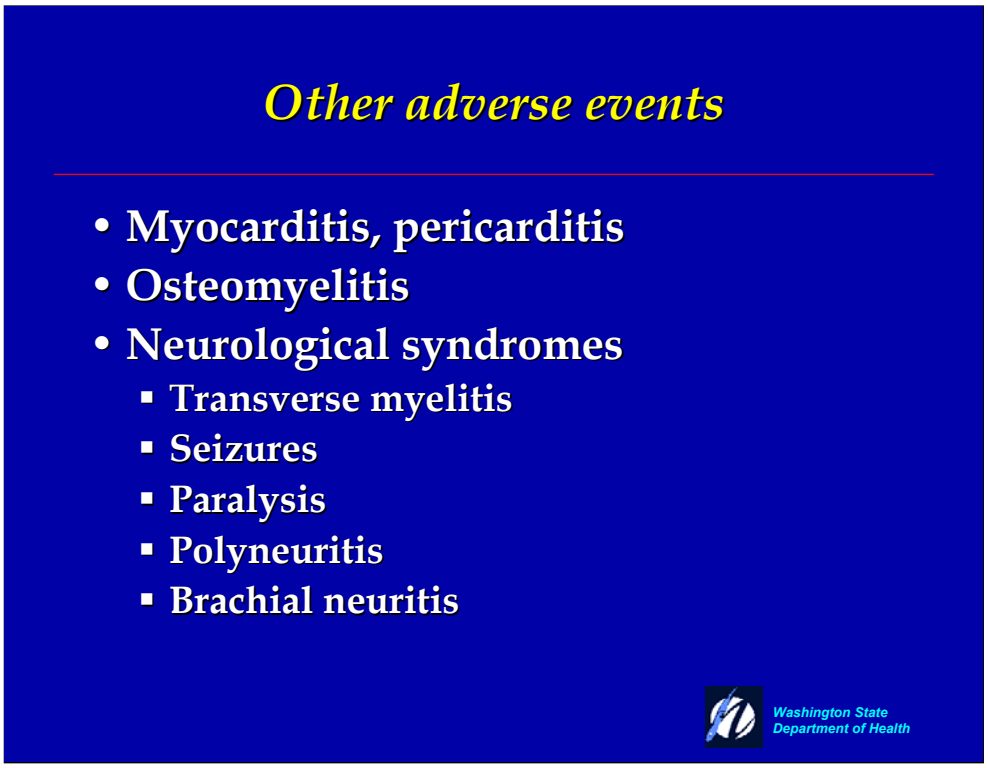
Fetal vaccinia



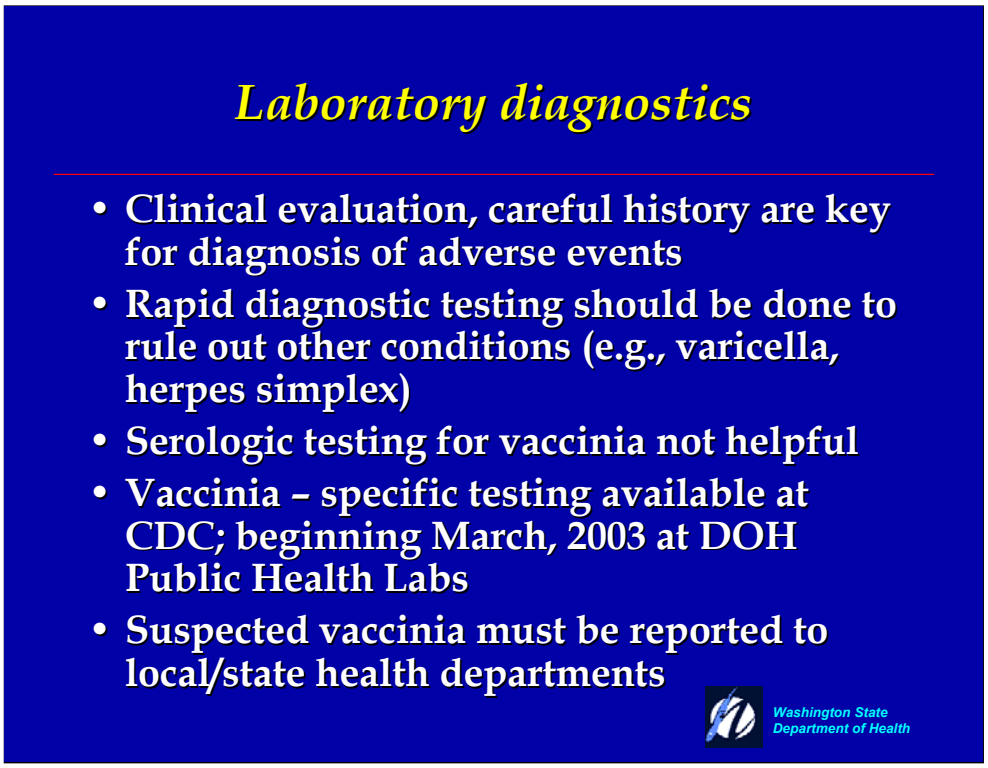
This is a neonate with fetal vaccinia – the characteristic lesions may be sparse or widespread, and it is not known if infection occurs from maternal viremia or through contact with the virus in amniotic fluid.



There is no reliable diagnostic test for fetal vaccinia, which usually results in death, either intrauterine or in the early post-natal period. There is limited experience with the use of vaccinia immune globulin, but it may be considered in a live infant born with characteristic lesions to a mother who was vaccinated, or in contact with a vaccinee, during pregnancy.



Other extremely rare adverse events that have been reported in association with vaccinia vaccine, including myocarditis, pericarditis, and osteomyelitis. Reported neurological syndromes include transverse myelitis, seizures, paralysis, polyneuritis and brachial neuritis.

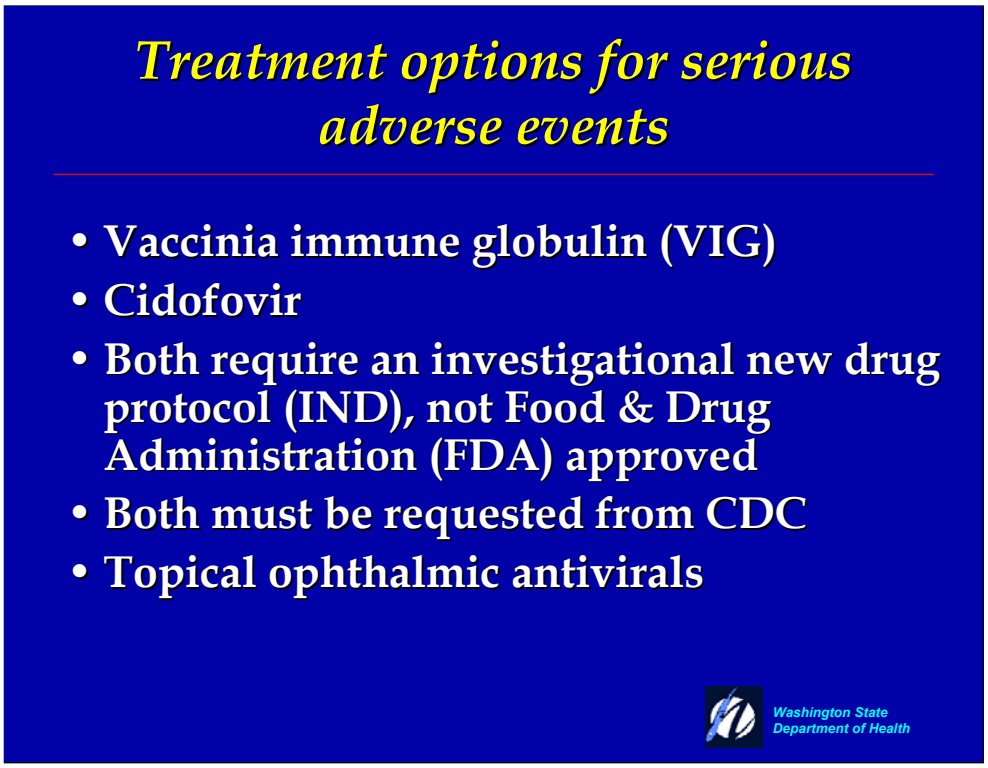


Laboratory diagnostics don't play much of a role in the diagnosis of smallpox vaccine adverse events. Clinical evaluation and a careful history are key to the diagnosis of smallpox vaccine adverse events. In patients who have recently been vaccinated, or may have had contact with a smallpox vaccinee, the presentation may be obvious, and there will be no need for specific diagnostic testing.

However, not all patients will be aware of their exposure and for some adverse events like generalized vaccinia, or eczema vaccinatum, the rash may be difficult to distinguish from those caused by other viruses when a history of vaccination or exposure is not elicited. In those circumstances, rapid diagnostic tests for varicella and herpes, either direct fluorescent antibody (DFA) or polymerase chain reaction assays (PCR), should be obtained to rule out these infections. Serologic testing is not helpful in the diagnosis of vaccinia infections.

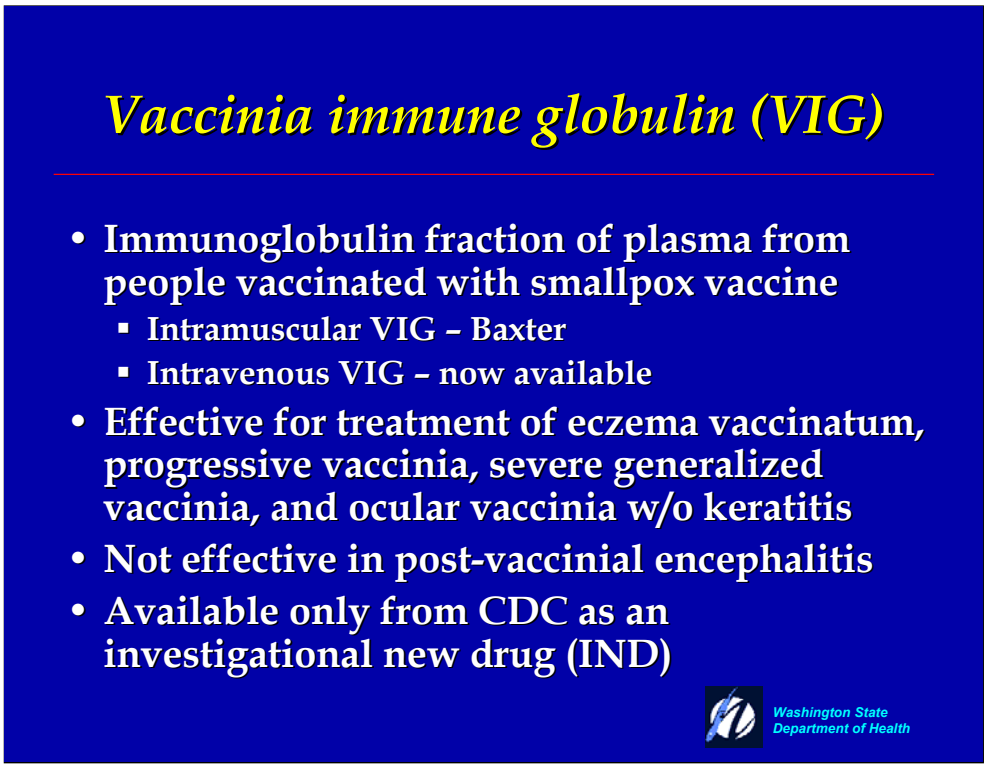
Vaccinia specific testing requires polymerase chain reaction assay, electron microscopy capabilities, or isolation of the virus in a biosafety level 3 lab; these are all currently available at CDC for appropriate samples. The WA State Department of Health Public Health Laboratories will be able to perform PCR for vaccinia beginning in March of this year.

Suspected cases of vaccinia should be reported immediately to your local health department and the WA State Department of Health Office of Epidemiology, to assure proper collection and transport of specimens for laboratory testing, if needed.



Treatment options for serious adverse events related to smallpox vaccine are limited to vaccinia immune globulin, or VIG and the parenteral antiviral cidofovir. Both VIG and cidofovir require an investigational new drug (IND) protocol for the treatment of vaccinia complications, as neither are licensed by the Food & Drug Administration for this indication. Both VIG and cidofovir must be approved for use and requested from CDC, which I will discuss in more detail later.

Topical ophthalmic preparations of antivirals are available, but data on their efficacy is limited.

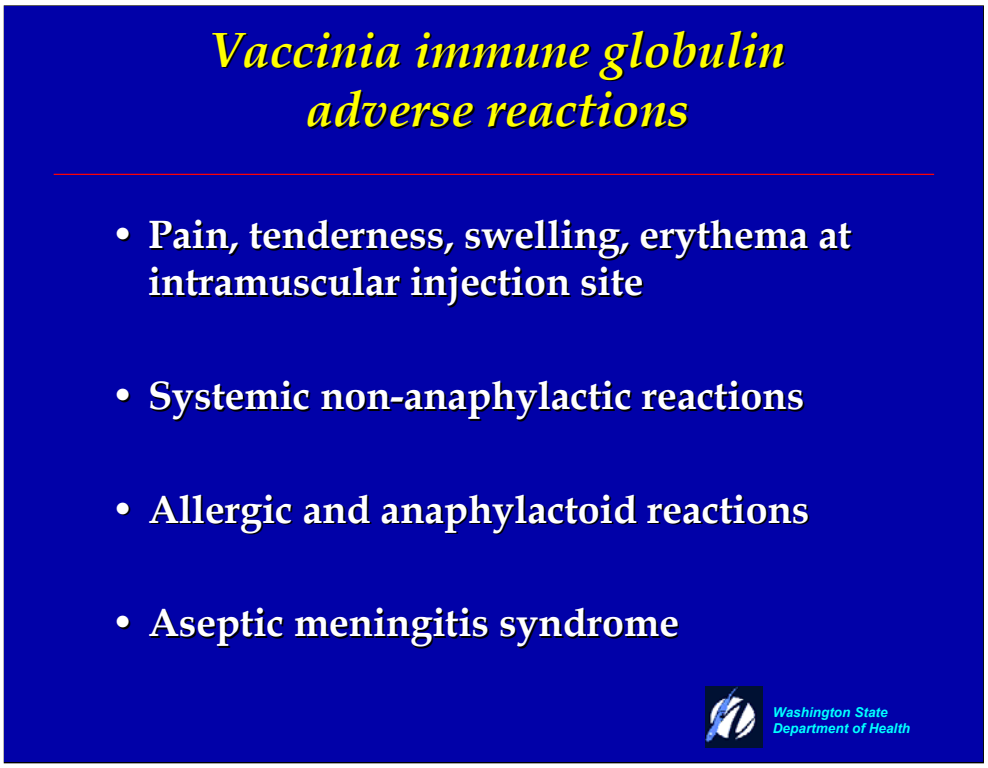


Vaccinai immune globulin (VIG) is a sterile solution of the immunoglobulin fraction of plasma obtained from people who have received multiple doses of smallpox vaccine. The IM formulation of VIG (Baxter Healthcare Corp, 1994) is given intramuscularly and contains trace amounts of thimerosal as a preservative. An intravenous formulation is also available and does not contain thimerosal.

VIG is effective for smallpox adverse events caused by continued viral replication – EV, PV, severe GV, and cases of ocular vaccinia. The use of VIG in ocular vaccinia with keratitis may increase the risk for corneal scarring.

VIG is not effective in post-vaccinial encephalitis.

VIG is available only from the CDC as an investigational new drug.



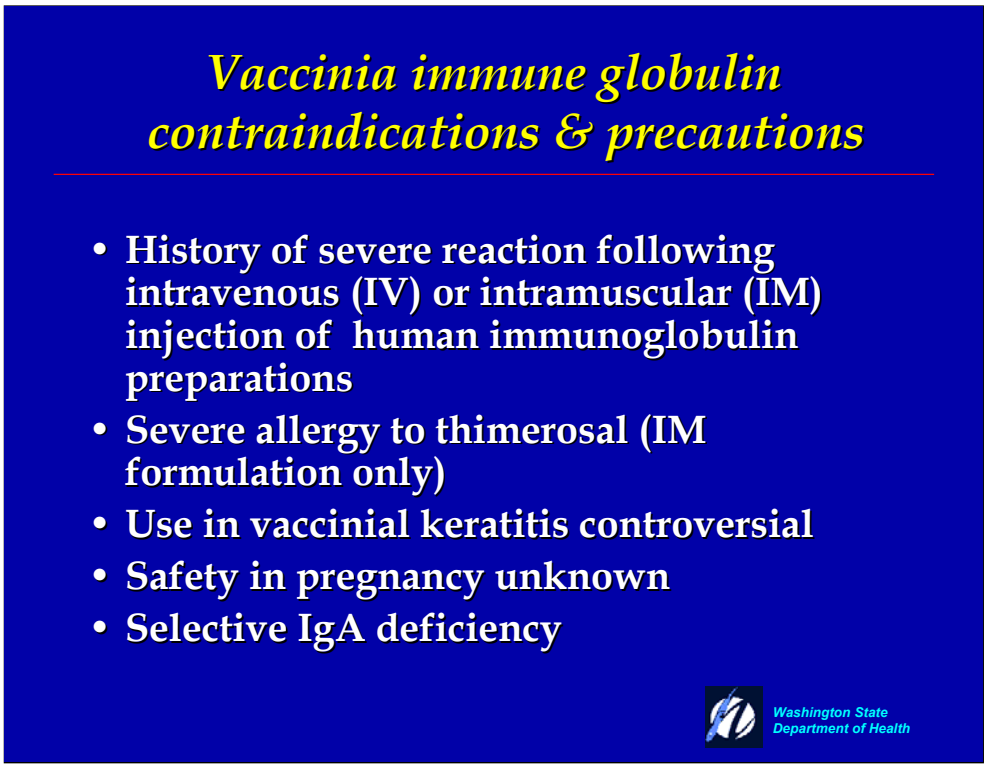
Adverse reactions associated with VIG are similar to those seen with the use of other immunoglobulins. Pain, tenderness, swelling, and erythema at the IM injection site may persist for 1-2 days after administration. This is not a problem with intravenous VIG

Other moderate adverse events include a systemic non-anaphylactic reaction with joint, back, and abdominal pain, myalgias, nausea, vomiting, diarrhea, chills, fever, headache, and rash. This will subside within several hours of the end of the infusion with IV administration. Pretreatment with corticosteroids and acetaminophen may help alleviate these symptoms.

More serious adverse events associated with the administration of VIG include hypotension, anaphylaxis and anaphylactoid reactions, renal dysfunction and aseptic meningitis syndrome. Hypotension, and immediate allergic reactions may begin within seconds to hours after infusion, and the treatment is the same as for any acute allergic reaction: immediate d/c of VIG, and administration of epinephrine, oxygen, antihistamines, corticosteroids and cardiorespiratory support.

The onset of aseptic meningitis syndrome is within hours to days after infusion and is characterized by a severe headache, stiff neck, fever, photophobia, nausea & vomiting. D/c of VIG will result in remission of symptoms within days.

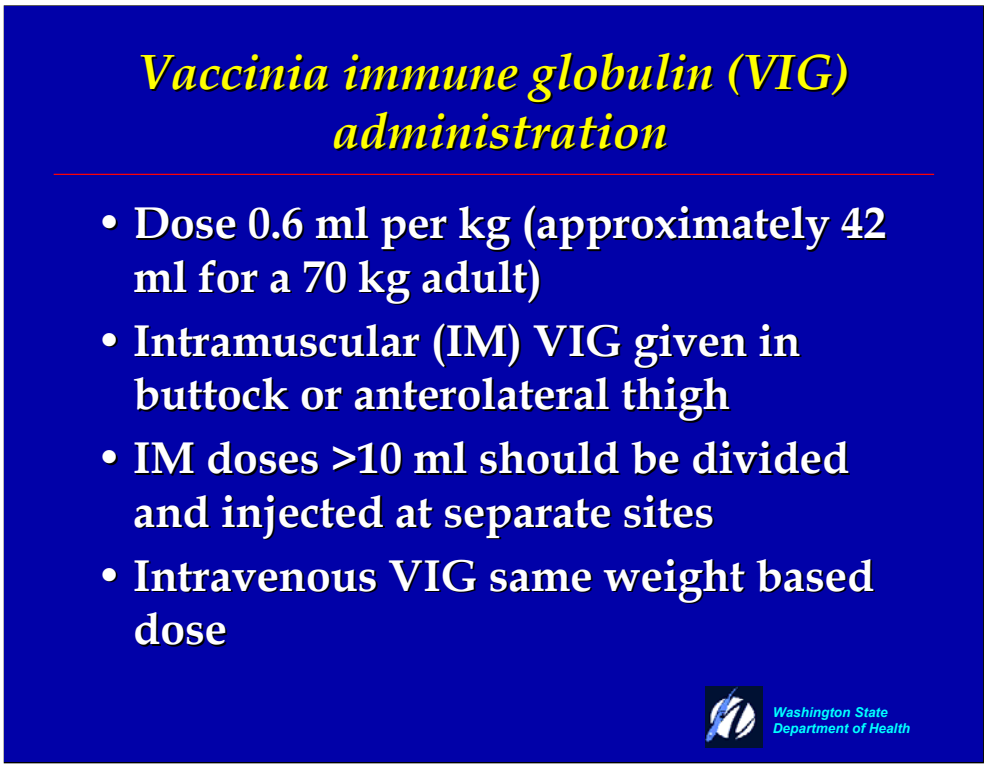
As with any product derived form human blood, the possibility of transmission of blood borne pathogens cannot be completely excluded. The current IV products undergo the same controls currently used at all blood & plasma donor facilities in the United States.



Contraindications for VIG include an allergic reaction following administration of human immunoglobulin preparations, or for the IM product, to thimerosal.

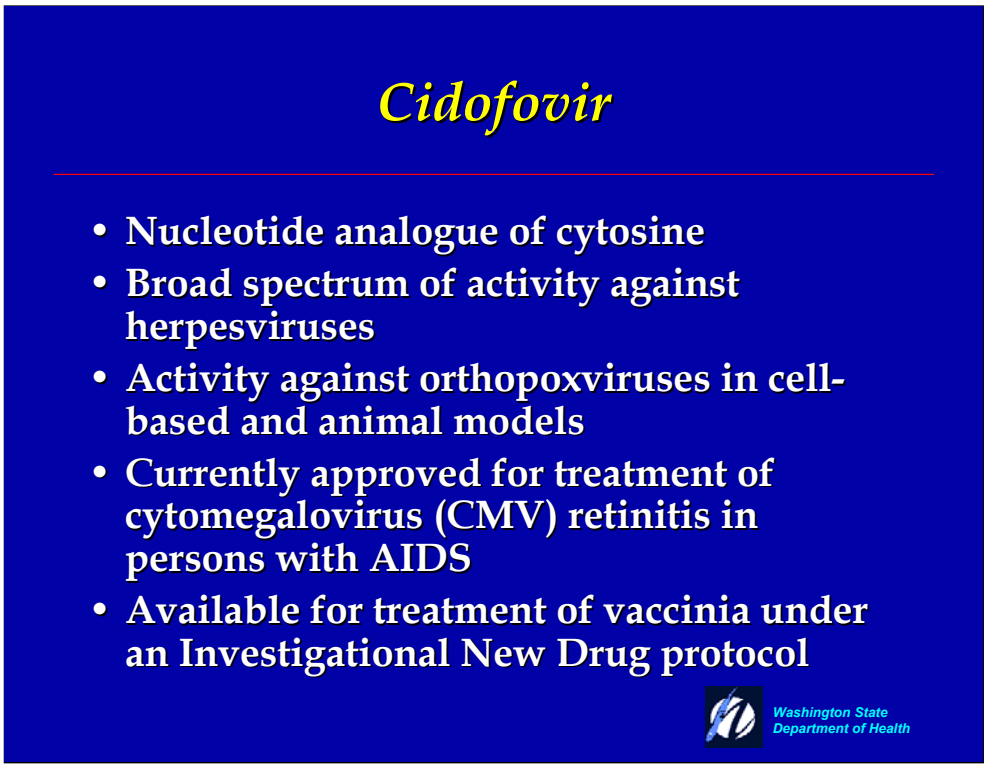
The use of VIG in vaccinial keratitis is controversial. And the safety of its use in pregnancy is unknown.

Finally, some people with selective IgA antibodies who receive IG products may develop an anaphylactoid reaction if they receive blood products containing IgA.



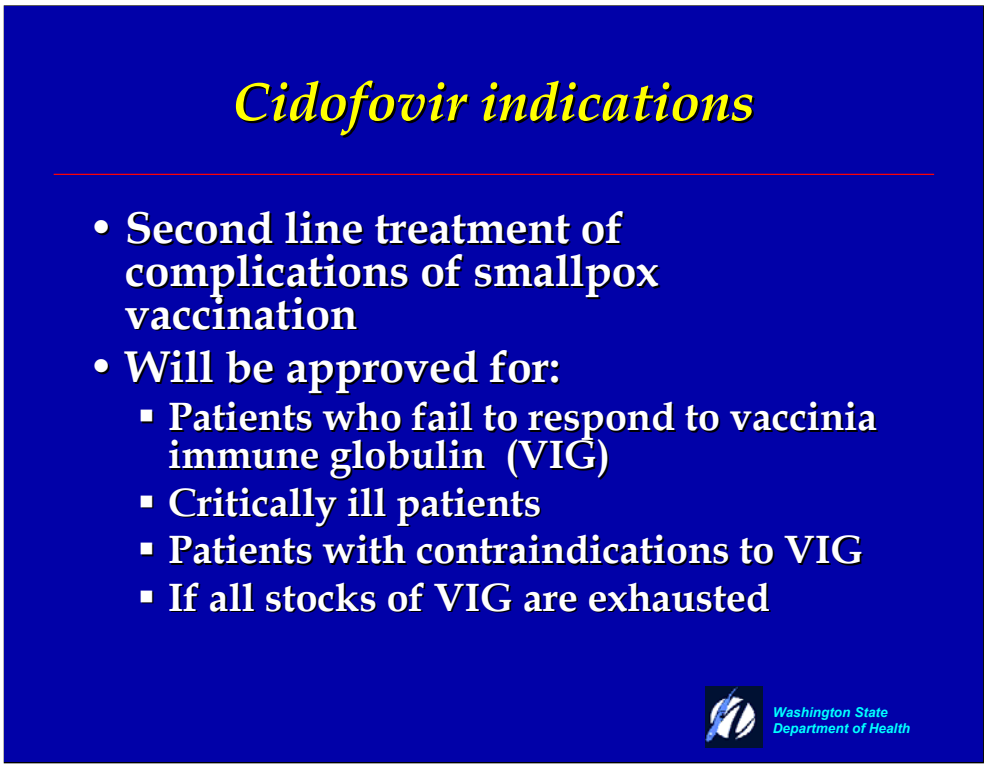
Detailed instructions on VIG administration are included in the insert that accompanies the Investigational New Drug (IND) materials shipped with the product, whether it is the IV or IM formulation. The dose is 0.6 mL/kg. IM VIG is given in the buttock or anterolateral thigh, and doses should be divided into 10 mL aliquots and injected at separate sites.

IV VIG is the same weight based dose, 0.6 mL/kg.

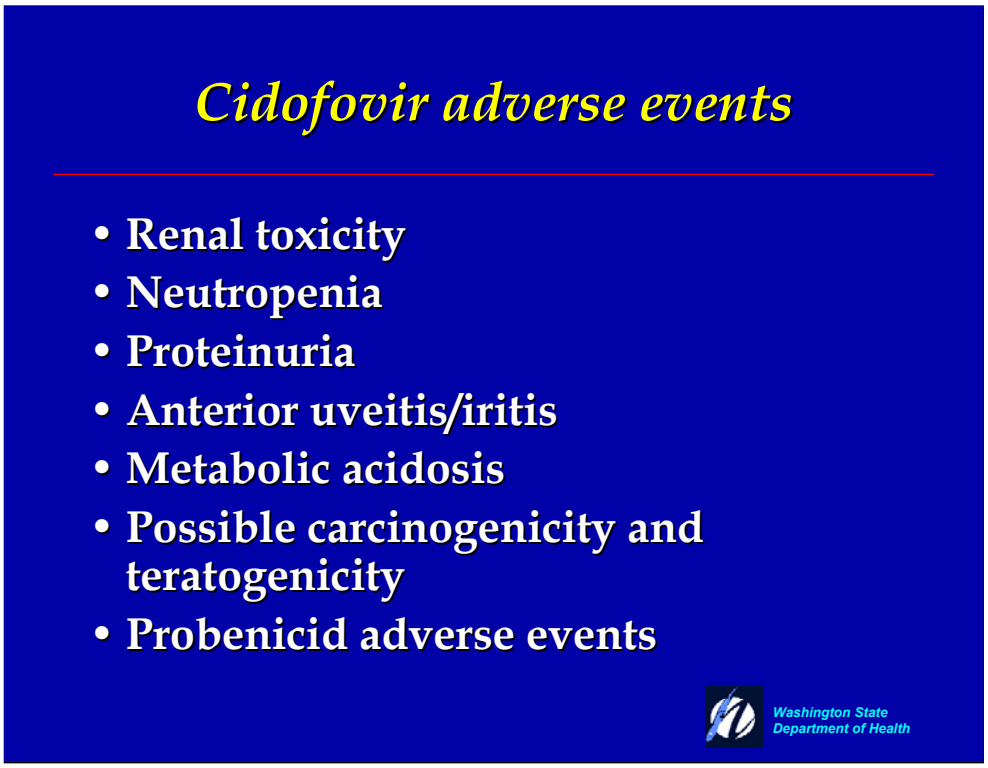


Cidofovir, is an nucleoside analogue of cytosine, and has a broad spectrum of activity against herpesviruses. In cell-based and animal models, it also has activity against certain orthopoxviruses, the family containing both smallpox and vaccinia. But its efficacy in the treatment of vaccinia-related complications in humans is unknown.

Cidofovir is currently approved by the FDA for the treatment of cytomegalovirus retinitis in patients with AIDS, but it will be available from CDC for the treatment of vaccinia in humans under an IND. Because of renal toxicity, cidofovir must be given with adequate hydration and probenecid.

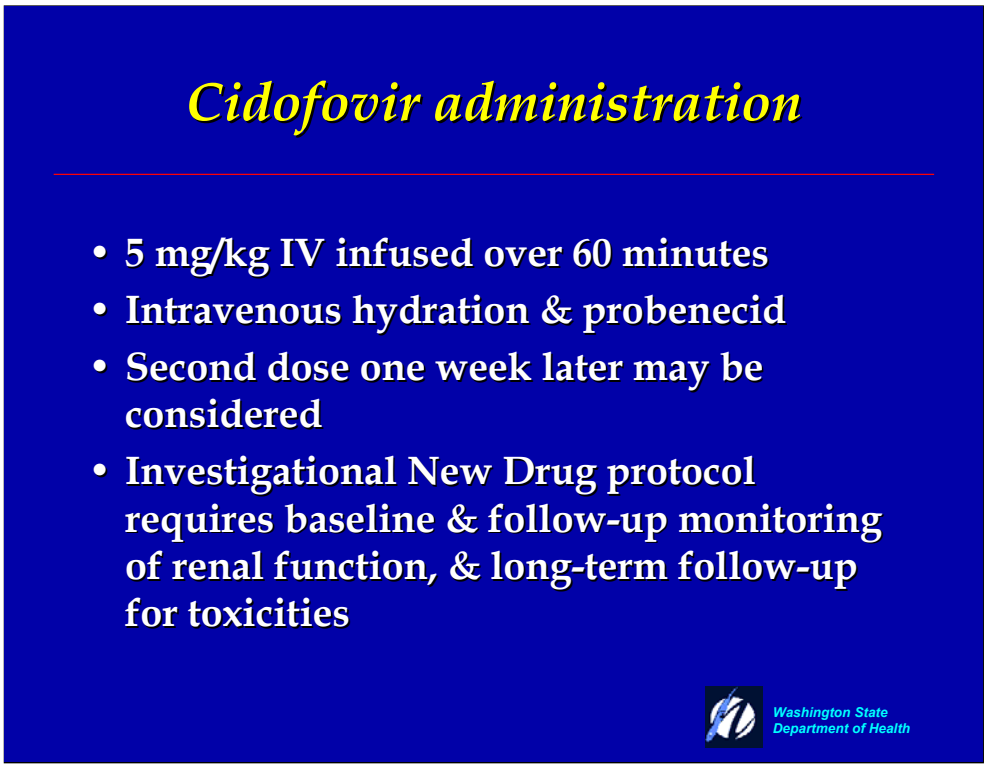


Because of its unclear efficacy for vaccinia, and its known toxicities, cidofovir is second line therapy and will only be released from CDC for investigational new drug (IND) use if a patient fails to respond to vaccinia immune globulin (VIG) treatment, is critically ill, has contraindications to VIG, or if all stocks of VIG have been exhausted.



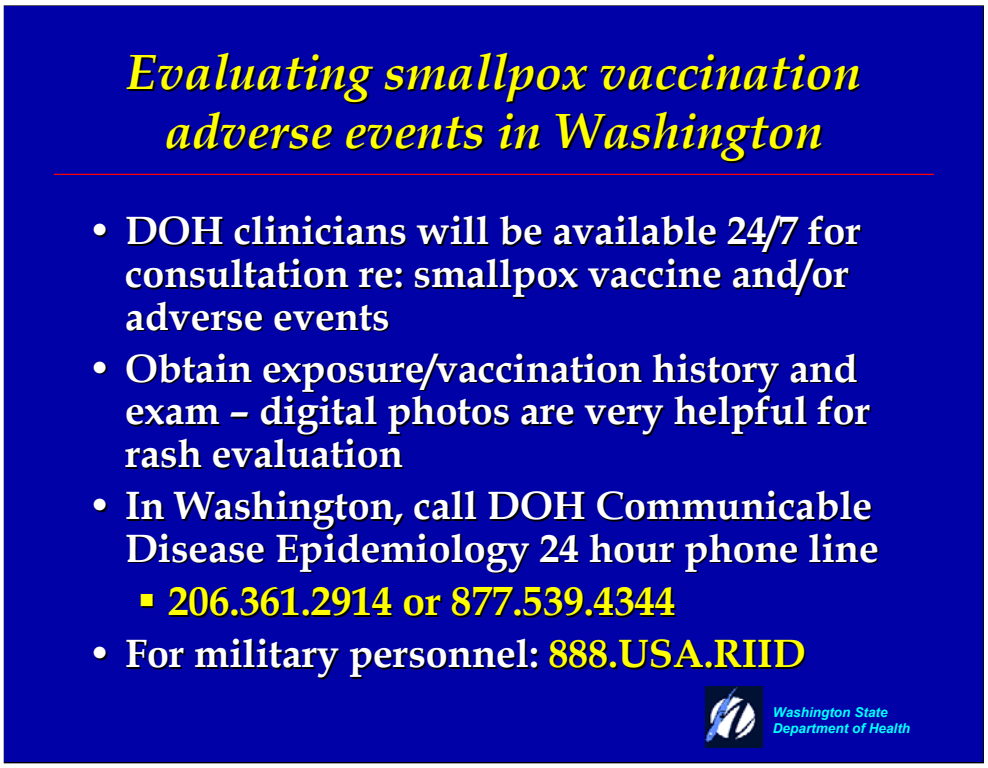
Adverse events associated with cidofovir include renal toxicity, which may be irreversible, neutropenia, proteinuria, uveitis, iritis, and metabolic acidosis. Animal studies have found carcinogenicity and teratogenicity.

In addition, side effects associated with probenecid include: headache, nausea, vomiting, gout and uric acid stones; more serious AEs include hemolytic anemia, hepatic necrosis, and aplastic anemia



Details for administration will be included in the package insert with the Investigational New Drug materials. The dose is 5 mg/kg IV infused over 60 minutes, with IV hydration and probenecid. A second dose should be considered a week later later if there is no response to the first dose.

The IND protocol requires baseline and follow-up monitoring of renal function, as well as viral cultures. Long-term follow-up (6 months) is required to assess outcome and toxicities

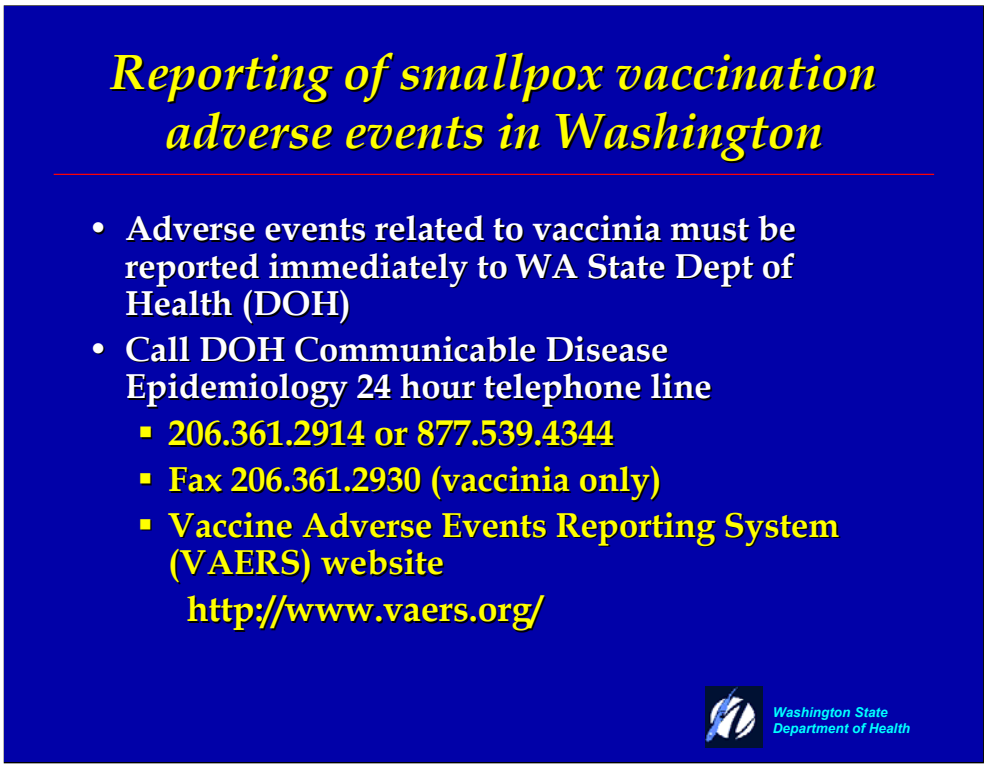


DOH clinicians will be available 24 hours a day, 7 days a week for consultation on smallpox vaccine & suspected adverse events, and to provide assistance in contacting CDC's Clinical Consulting Team if the case is complex or requires treatment with vaccinia immune globulin (VIG) or cidofovir.

Health care providers who suspect an adverse event should obtain a thorough vaccination or exposure history and physical exam, and if possible, obtain digital photographs, with consent of the patient, of any dermatologic manifestations. These photos are very helpful for rash evaluation and can be transmitted to consulting clinicians. This information will speed the consultation and decisions regarding the need for diagnostic testing and referral for VIG or cidofovir.

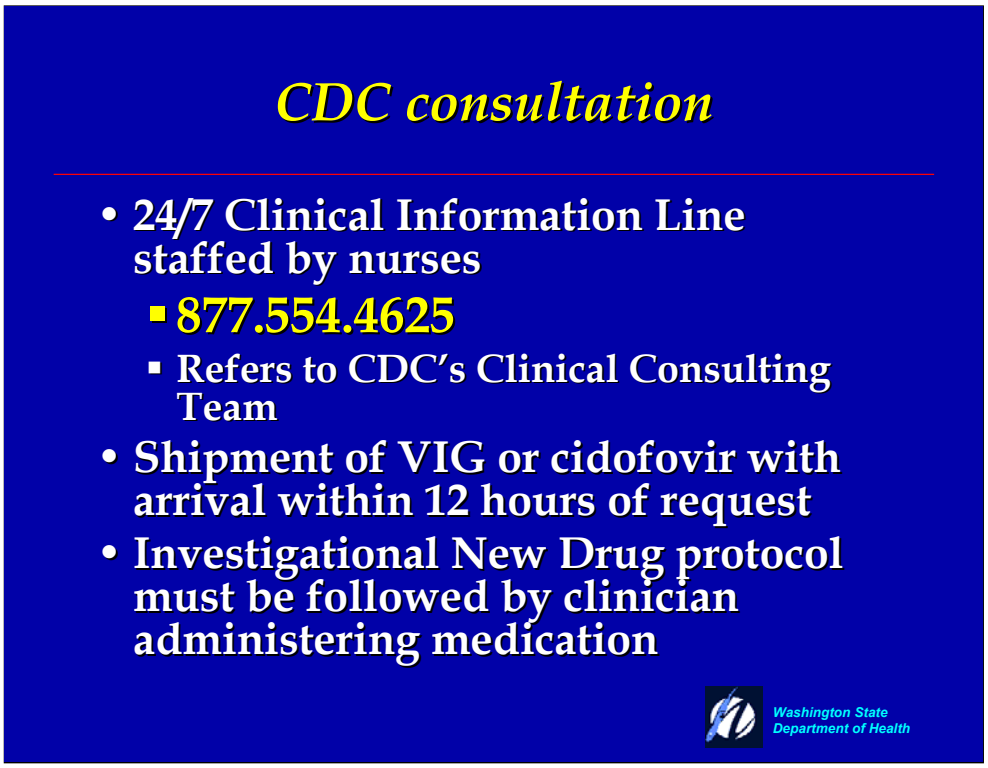
In WA, call DOH Communicable Diseases Epidemiology's 24 hour telephone lines – listed on the slide.

For questions re: vaccination or adverse events in military personnel, calls should be referred to the Department of Defense hotline @ 888.USA.RIID



Suspected adverse events related to vaccinia should be reported immediately by telephone to the state health department, unless you are instructed by your local health department to report adverse events directly to their office. Adverse events can be reported by telephone to the DOH Communicable Disease Epidemiology 24 hour telephone line.

Reports can also be submitted using Vaccine Adverse Events Reporting System, or VAERS forms by FAX to 206.361.2930, or electronically on the VAERS website. However, when reporting via the web, it is also important to fax a copy of the VAERS report directly to DOH or your local health department within 24 hours of diagnosis.



As a back-up, CDC will provide a 24/7 Clinical Information Line for clinical consultation, staffed by RNs to triage calls from clinicians with questions about vaccine and vaccine adverse events. This line will also refer callers with suspected serious adverse events to the CDC Clinical Consulting Team as needed.

The Clinical Consulting Team will make a determination about need for VIG or cidofovir, and will arrange of the immediate shipment of either, with IND materials from CDC to the requesting clinician. Shipments should arrive within 12 hours of the request via the National Pharmaceutical Stockpile, which is sufficient time to initiate treatment.

The Investigational New Drug protocol must be followed by clinicians administering the VIG or cidofovir, including completion of the accompanying paperwork.

CDC is also developing specific evaluation and treatment protocols for management of serious adverse events, which will be available on their smallpox website.

Here are some useful Websites – CDC's smallpox webpage, their clinical evaluation tool website, the Vaccine Adverse Events Reporting System website and the DOH website, where you can get additional information about adverse events recognition, management and reporting. Thanks and now I will be taking questions.


Images from:
Centers for Disease Control & Prevention
Sally Abbott, ARNP
Dr. John Leedom
Dr. J. Michael Lane
Dr. Vincent Fulginiti
World Health Organization
University of Rochester
National Institutes of Health
Logical Images, Inc.
New England Journal of Medicine
Washington State
Department of Health